No. 23-10362

IN THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

ALLIANCE FOR HIPPOCRATIC MEDICINE; AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS; AMERICAN COLLEGE OF PEDIATRICIANS; CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS; SHAUN JESTER, D.O.; REGINA FROST-CLARK, M.D.; TYLER JOHNSON, D.O.; GEORGE DELGADO, M.D.,

Plaintiffs-Appellees,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, Commissioner of Food and Drugs; JANET WOODCOOK, M.D., in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration; PATRIZIA CAVAZZONI, M.D., in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, Secretary, U.S. Department of Health and Human Services,

Defendants-Appellants,

DANCO LABORATORIES, L.L.C.,

Intervenor-Appellant.

ADDENDUM TO EMERGENCY MOTION FOR A STAY PENDING APPEAL

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FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

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MEMORANDUM OPINION AND ORDER

Before the Court is Plaintiffs' Motion for Preliminary Injunction ("Motion") (ECF No. 6), filed on November 18, 2022. The Court **GRANTS** the Motion **IN PART**.

BACKGROUND

Over twenty years ago, the United States Food and Drug Administration ("FDA") approved chemical abortion ("2000 Approval"). The legality of the 2000 Approval is now before this Court. Why did it take *two decades* for judicial review in federal court? After all, Plaintiffs' petitions challenging the 2000 Approval date back to the year 2002, right?

Simply put, FDA stonewalled judicial review — until now. Before Plaintiffs filed this case, FDA ignored their petitions for over sixteen years, even though the law requires an agency response within "180 days of receipt of the petition." 21 C.F.R. § 10.30(e)(2)). But FDA waited 4,971 days to adjudicate Plaintiffs' first petition and 994 days to adjudicate the second. *See* ECF Nos. 1-14, 1-28, 1-36, 1-44 ("2002 Petition," "2019 Petition," respectively). Had FDA responded to Plaintiffs' petitions within the 360 total days allotted, this case would have been in federal court *decades* earlier. Instead, FDA postponed and procrastinated for nearly **6,000 days**.

Plaintiffs are doctors and national medical associations that provide healthcare for pregnant and post-abortive women and girls. Plaintiffs sued Defendants to challenge multiple administrative actions culminating in the 2000 Approval of the chemical abortion regimen for mifepristone. ECF No. 1 at 2. Mifepristone — also known as RU-486 or Mifeprex — is a synthetic steroid that blocks the hormone progesterone, halts nutrition, and ultimately starves the unborn human until death. ECF No. 7 at 7–8.[1] Because mifepristone alone will not always complete the abortion, FDA mandates a two-step drug regimen: mifepristone to kill the unborn human, followed by misoprostol to induce cramping and contractions to expel the unborn human from the mother's womb. *Id.* at 8.

In 1996, the Population Council[2] filed a new drug application ("NDA") with FDA for mifepristone. ECF No. 1 at 35. Shortly thereafter, FDA reset the NDA from "standard" to "priority review." *Id.* In February 2000, FDA wrote a letter to the Population Council stating that "adequate information ha[d] *not* been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for use as recommended." ECF No. 1-24 at 6 (emphasis added). FDA also noted the "restrictions on distribution will need to be amended." *Id.*

[1] Jurists often use the word "fetus" to inaccurately identify unborn humans in *un*scientific ways. The word "fetus" refers to a specific gestational stage of development, as opposed to the zygote, blastocyst, or embryo stages. *See* ROBERT P. GEORGE & CHRISTOPHER TOLLEFSEN, EMBRYO 27–56 (2008) (explaining the gestational stages of an unborn human). Because other jurists use the terms "unborn human" or "unborn child" interchangeably, and because both terms are inclusive of the multiple gestational stages relevant to the FDA Approval, 2016 Changes, and 2021 Changes, this Court uses "unborn human" or "unborn child" terminology throughout this Order, as appropriate.

[2] The Population Council was founded by John D. Rockefeller in 1952 after he convened a conference with "population activists" such as Planned Parenthood's director and several well-known eugenicists. MATTHEW CONNELLY, FATAL MISCONCEPTION: THE STRUGGLE TO CONTROL WORLD POPULATION 156 (2008). The conference attendees discussed "the problem of 'quality.'" John D. Rockefeller, *On the Origins of the Population Council*, 3 POPULATION AND DEV. REV. 493, 496 (1977). They concluded that "[m]odern civilization had reduced the operation of natural selection by saving more 'weak' lives and enabling them to reproduce," thereby resulting in "a downward trend in . . . genetic quality." *Id.*

Mere months later, FDA approved the chemical abortion regimen under Subpart H, commonly known as "accelerated approval" and originally designed to expedite investigational HIV medications during the AIDS epidemic.[3] Subpart H accelerates approval of drugs "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (*e.g.*, ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)." 21 C.F.R. § 314.500.

FDA then imposed post-approval restrictions "to assure safe use." *See* 21 C.F.R. § 314.520. These restrictions were later adopted when Subpart H was codified as a Risk Evaluation and Mitigation Strategy ("REMS") "to ensure that the benefits of the drug outweigh the risks." 21 U.S.C. § 355-1(a)(1)–(2). The drugs were limited to women and girls with unborn children aged seven-weeks gestation or younger. ECF No. 7 at 9. FDA also required three (3) in-person office visits: the first to administer mifepristone, the second to administer misoprostol, and the third to assess any complications and ensure there were no fetal remains in the womb. *Id.* Additionally, abortionists were required to be properly trained to administer the regimen and to report *all* adverse events from the drugs. *Id.*

Plaintiffs American Association of Pro-Life Obstetricians & Gynecologists ("AAPLOG") and Christian Medical & Dental Associations filed the 2002 Petition with FDA challenging the 2000 Approval. *Id.* In 2006, the U.S. House Subcommittee on Criminal Justice, Drug Policy, and Human Resources expressed the same concerns and held a hearing to investigate FDA's handling

[3] *See, e.g.*, Jessica Holden Kloda & Shahza Somerville, *FDA's Expedited Review Process: The Need for Speed*, 35 APPLIED CLINICAL TRIALS 17, 17–18 (2015) ("In 1992, in response to a push by AIDS advocates to make the investigational anti-AIDS drug azidothymidine (AZT) accessible, the FDA enacted 'Subpart H' commonly referred to as accelerated approval; giving rise to expedited review of drugs by the FDA.").

of mifepristone and its subsequent monitoring of the drug.[4] Then-Chairman Souder remarked that mifepristone was "associated with the deaths of at least 8 women, 9 life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection."[5] Additionally, Chairman Souder noted "more than 950 adverse event cases" associated with mifepristone "out of only 575,000 prescriptions, at most."[6] The subsequent Staff Report concluded that FDA's approval and monitoring of mifepristone was "substandard and necessitates the withdrawal of this dangerous and fatal product before more women suffer the known and anticipated consequences or fatalities."[7] The report stated the "unusual approval" demonstrated a lower standard of care for women, "and [mifepristone's] withdrawal from the market is justified and necessary to protect the public's health."[8]

FDA rejected the 2002 Petition on March 29, 2016 — nearly *fourteen* years after it was filed. ECF No. 7 at 9. That same day, FDA approved several changes to the chemical abortion drug regimen, including the removal of post-approval safety restrictions for pregnant women and girls. *Id.* at 10. FDA increased the maximum gestational age from seven-weeks gestation to ten-weeks gestation. *Id.* And FDA also: (1) changed the dosage for chemical abortion; (2) reduced the number of required in-person office visits from three to one; (3) allowed non-doctors to prescribe and administer chemical abortions; and (4) eliminated the requirement for prescribers to report non-fatal adverse events from chemical abortion. *Id.*

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[4] *See The FDA and RU-486: Lowering the Standard for Women's Health: Hearing Before the Subcomm. on Crim. Just., Drug Pol'y, & Hum. Res. of the H. Comm. on Gov't Reform*, 109th Cong. 3 (2006) ("Subcommittee Report").

[5] The transcript of the hearing before the House Subcommittee is available at https://www.govinfo.gov/content/pkg/CHRG-109hhrg31397/html/CHRG-109hhrg31397.htm.

[6] *Id.*

[7] Subcommittee Report at 40.

[8] *Id.*

In March 2019, Plaintiffs AAPLOG and American College of Pediatricians filed the 2019 Petition challenging FDA's 2016 removal of safety restrictions. *Id.* On April 11, 2019, FDA approved GenBioPro, Inc.'s abbreviated new drug application ("ANDA") for a generic version of mifepristone without requiring or reviewing *new* peer-reviewed science ("2019 Generic Approval"). *Id.* Two years later, on April 12, 2021, FDA announced it would "exercise enforcement discretion" to allow "dispensing of mifepristone through the mail . . . or through a mail-order pharmacy" during the COVID pandemic — notwithstanding the nearly 150-year-old Comstock Act banning the *mailing* of "[e]very article, instrument, substance, drug, medicine or thing" that produces "abortion." *Id.* Finally, on December 16, 2021, FDA denied most of Plaintiff's 2019 Petition. *Id.* at 11. Specifically, FDA expressly rejected the 2019 Petition's request to keep the in-person dispensing requirements and announced that the agency would *permanently* allow chemical abortion by mail. *Id.*

After Plaintiffs filed suit, Danco Laboratories, LLC ("Danco") — the holder of the NDA for mifepristone — moved to intervene as a defendant. ECF No. 19. On February 6, 2023, this Court granted Danco's motion. ECF No. 33. Plaintiffs now seek a preliminary injunction ordering Defendants to withdraw or suspend: (1) FDA's 2000 Approval and 2019 Approval of mifepristone tablets, 200 mg, thereby removing both from the list of Approved Drugs; (2) FDA's 2016 Changes and 2019 Generic Approval; and (3) FDA's April 12, 2021, Letter and December 16, 2021, Response to the 2019 Petition concerning the in-person dispensing requirement for mifepristone. ECF No. 7 at 12. Additionally, Plaintiffs seek to enjoin Defendants from taking actions inconsistent with these orders. *Id.*

LEGAL STANDARD

A court may issue a preliminary injunction when a movant satisfies the following four factors: (1) a substantial likelihood of success on the merits; (2) a substantial threat of irreparable harm if the injunction does not issue; (3) the threatened injury outweighs any harm that will result if the injunction is granted; and (4) the grant of an injunction is in the public interest. *See Louisiana v. Becerra*, 20 F.4th 260, 262 (5th Cir. 2021). "The purpose of a preliminary injunction is always to prevent irreparable injury so as to preserve the court's ability to render a meaningful decision on the merits." *Canal Auth. of State of Fla. v. Callaway*, 489 F.2d 567, 576 (5th Cir. 1974). The same standards apply "to prevent irreparable injury" under the Administrative Procedure Act ("APA"). *See* 5 U.S.C. § 705; *Wages & White Lion Invs., L.L.C. v. U.S. Food & Drug Admin.*, 16 F.4th 1130, 1143 (5th Cir. 2021).

ANALYSIS

A. Plaintiffs Have Standing

The judicial power of federal courts is limited to certain "Cases" and "Controversies." U.S. CONST. art. III, § 2. The case-or-controversy requirement requires a plaintiff to establish he has standing to sue. *See Cibolo Waste, Inc. v. City of San Antonio*, 718 F.3d 469, 473 (5th Cir. 2013). To have standing, the party invoking federal jurisdiction must show: "(i) that he suffered an injury in fact that is concrete, particularized, and actual or imminent; (ii) that the injury was likely caused by the defendant; and (iii) that the injury would likely be redressed by judicial relief." *TransUnion LLC v. Ramirez*, 141 S. Ct. 2190, 2203 (2021). Courts should assess whether the alleged injury to the plaintiff has a "close relationship" to harm "traditionally" recognized as providing a basis for a lawsuit in American courts. *Id.* at 2204. "[S]tanding is not dispensed in

gross; rather, plaintiffs must demonstrate standing for each claim that they press and for each form of relief that they seek (for example, injunctive relief and damages)." *Id.* at 2208.

1. Plaintiff Medical Associations have Associational Standing

"An association or organization can establish an injury-in-fact through either of two theories, appropriately called 'associational standing' and 'organizational standing.'" *OCA-Greater Hous. v. Texas*, 867 F.3d 604, 610 (5th Cir. 2017). Under a theory of "associational standing," an association "has standing to bring a suit on behalf of its members when its members would otherwise have standing to sue in their own right, the interests at stake are germane to the organization's purpose, and neither the claim asserted nor the relief requested requires the participation of individual members in the lawsuit." *Tex. Ass'n of Mfrs. v. U.S. Consumer Prod. Safety Comm'n*, 989 F.3d 368, 377 (5th Cir. 2021) (quoting *Friends of the Earth, Inc. v. Laidlaw Env't Servs. (TOC), Inc.*, 528 U.S. 167, 181 (2000)).

Here, the associations' members have standing because they allege adverse events from chemical abortion drugs can overwhelm the medical system and place "enormous pressure and stress" on doctors during emergencies and complications.[9] ECF No. 7 at 14. These emergencies "consume crucial limited resources, including blood for transfusions, physician time and attention, space in hospital and medical centers, and other equipment and medicines." ECF No. 1-5 at 9. This is especially true in maternity-care "deserts" — geographical areas with limited physician availability. *Id.* These emergencies force doctors into situations "in which they feel complicit in the elective chemical abortion by needing to remove a baby with a beating heart or pregnancy

[9] *See* James Studnicki et al., *A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999-2015*, 8 HEALTH SERV. RSCH. MGMT. EPIDEMIOLOGY 8 (2021) ("ER visits following mifepristone abortion grew from 3.6% of all postabortion visits in 2002 to 33.9% of all postabortion visits in 2015. The trend toward increasing use of mifepristone abortion requires all concerned with health care utilization to carefully follow the ramifications of ER utilization.").

tissue as the only means to save the life of the woman or girl." ECF No. 1 at 85. Members of Plaintiff medical associations "oppose being forced to end the life of a human being in the womb for no medical reason, including by having to complete an incomplete elective chemical abortion." *Id.* at 86; *see also Texas v. Becerra*, No. 5:22-CV-185-H, 2022 WL 3639525, at *12 (N.D. Tex. Aug. 23, 2022) (unwanted participation in elective abortions is cognizable under Article III).

Plaintiffs also argue the challenged actions "prevent Plaintiff doctors from practicing evidence-based medicine" and have caused Plaintiffs to face increased exposure to allegations of malpractice and potential liability, along with higher insurance costs. ECF No. 7 at 15. The lack of information on adverse events "harms the doctor-patient relationship" because women and girls are prevented from giving informed consent to providers. *Id.*; *see also* American Medical Association Code of Medical Ethics, *Opinion 2.1.1: Informed Consent* (informed consent is "fundamental in both ethics and law"). To obtain informed consent, physicians must "[a]ssess the patient's ability to understand relevant medical information" and present to their patient "relevant information accurately and sensitively," including the burdens and risks of the procedure. *Id.*

Women also perceive the harm to the informed-consent aspect of the physician-patient relationship. In one study, fourteen percent of women and girls reported having received insufficient information about (1) side effects, (2) the intensity of the cramping and bleeding, (3) the next steps after expelling the aborted human, and (4) potential negative emotional reactions like fear, uncertainty, sadness, regret, and pain. *See* Katherine A. Rafferty & Tessa Longbons, *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives*, 36 HEALTH COMMC'N. 1485, 1485–94 (2021). Plaintiff physicians' lack of pertinent information on chemical abortion harms their physician-patient relationships because they *cannot* receive informed consent from the women and

girls they treat in their clinics. Plaintiffs allege these actions have "radically altered the standard of care." ECF No. 1-6 at 7.

Additionally, Plaintiff medical associations have associational standing via their members' third-party standing to sue on behalf of their patients. *See N.Y. State Club Ass'n, Inc. v. City of New York*, 487 U.S. 1, 9 (1988) ("It does not matter what specific analysis is necessary to determine that the members could bring the same suit."); *Pa. Psychiatric Soc. v. Green Spring Health Servs., Inc.*, 280 F.3d 278, 293 (3d Cir. 2002) ("So long as the association's members have or will suffer sufficient injury to merit standing and their members possess standing to represent the interests of third-parties, then associations can advance the third-party claims of their members without suffering injuries themselves."); *Ohio Ass'n of Indep. Schs. v. Goff*, 92 F.3d 419, 422 (6th Cir. 1996) (associational standing via member schools' third-party standing to assert constitutional rights of parents to direct their children's education); 13A Charles Alan Wright & Arthur R. Miller, *Federal Practice and Procedure* § 3531.9.3 (3d ed. 2022) ("Doctors regularly achieve standing to protect the rights of patients and their own related professional rights.").

The requirements for third-party standing are met here because: (1) the patients have "endure[d] many intense side effects and suffer[ed] significant complications requiring medical attention" and "suffer distress and regret";[10] (2) the patients have a "close relation" to the physician members of the Plaintiff medical associations; and (3) "some hindrance" exists to the patients' ability to protect their interests. *See* ECF No. 7 at 13; *Powers v. Ohio*, 499 U.S. 400, 410–11 (1991); *Singleton v. Wulff*, 428 U.S. 106, 117 (1976) (women seeking abortions may be chilled "by a desire to protect the very privacy of [their] decision from the publicity of a court suit");

[10] *Cf. TransUnion*, 141 S. Ct. at 2211 ("Nor did those plaintiffs present evidence that . . . they suffered some other injury (such as an emotional injury)"); *Denney v. Deutsche Bank AG*, 443 F.3d 253, 265 (2d Cir. 2006).

Pa. Psychiatric, 280 F.3d at 290 ("[A] party need not face insurmountable hurdles to warrant third-party standing."). The injuries suffered by patients of the Plaintiff medical associations' members are sufficient to confer associational standing.

Here, the physician-patient dynamic favors third-party standing. Unlike abortionists suing on behalf of women seeking abortions, here there are no potential conflicts of interest between the Plaintiff physicians and their patients. *See June Med. Servs. L.L.C. v. Russo*, 140 S. Ct. 2103, 2167 (2020) (Alito, J., dissenting), *abrogated by Dobbs v. Jackson Women's Health Org.*, 142 S. Ct. 2228 (2022) (abortionists have a "financial interest in avoiding burdensome regulations," while women seeking abortions "have an interest in the preservation of regulations that protect their health"). And the case for a close physician-patient relationship is even stronger here than in the abortion context. *See id.* at 2168 ("[A] woman who obtains an abortion typically does not develop a close relationship with the doctor who performs the procedure. On the contrary, their relationship is generally brief and very limited."); *see also* ECF No. 1-9 at 7 ("[I]n many cases there is no doctor-patient relationship [between a woman and an abortionist], so [women] often present to overwhelmed emergency rooms in their distress, where they are usually cared for by physicians other than the abortion prescriber."); ECF No. 1-11 at 4 (because there "is no follow-up or additional care provided to patients" by abortionists, there is "no established relationship with a physician" and "patients are simply left to report to the emergency room"). Plaintiff physicians often spend several hours treating post-abortive women, even hospitalizing them overnight or providing treatment throughout several visits. *See* ECF No. 1-8 at 5–6. Given the Supreme Court's jurisprudence on the close relationship between abortionists and women, the facts of this case indicate that Plaintiffs' relationships with their patients are at least as close — if not closer — for purposes of third-party standing.

Finally, women who have *already* obtained an abortion may be *more* hindered than women who challenge restrictions on abortion. Women who have aborted a child — especially through chemical abortion drugs that necessitate the woman seeing her aborted child once it passes — often experience shame, regret, anxiety, depression, drug abuse, and suicidal thoughts because of the abortion. *See* ECF No. 96 at 25; David C. Reardon et al., *Deaths Associated with Pregnancy Outcome: A Record Linkage Study of Low Income Women*, 95 S. MED. J. 834, 834–41 (2002) (women who receive abortions have a 154% higher risk of death from suicide than if they gave birth, with persistent tendencies over time and across socioeconomic boundaries, indicating "self-destructive tendencies, depression, and other unhealthy behavior aggravated by the abortion experience"); Priscilla K. Coleman, *Abortion and Mental Health: Quantitative Synthesis and Analysis of Research Published 1995–2009*, 199 BRITISH J. PSYCHIATRY 180, 180–86 (2011) (same). Subsequently, *in addition to* the typical privacy concerns present in third-party standing in abortion cases, adverse abortion experiences that are often deeply traumatizing pose a hindrance to a woman's ability to bring suit. In short, Plaintiffs — rather than their patients — are most likely the "least awkward challenger[s]" to Defendants' actions. *Craig v. Boren*, 429 U.S. 190, 197 (1976).

2. Plaintiff Medical Associations have Organizational Standing

"'[O]rganizational standing' does not depend on the standing of the organization's members." *OCA*, 867 F.3d at 610. The organization can establish standing in its own name if it "meets the same standing test that applies to individuals." *Id.* (internal marks omitted). An organization can have standing if it has "proven a drain on its resources resulting from counteracting the effects of the defendant's actions." *La. ACORN Fair Hous. v. LeBlanc*, 211 F.3d 298, 305 (5th Cir. 2000); *see also Zimmerman v. City of Austin, Tex.*, 881 F.3d 378, 390 (5th Cir.

2018) (changing one's "plans or strategies in response to an allegedly injurious law can itself be a sufficient injury to confer standing"). "Such concrete and demonstrable injury to the organization's activities—with the consequent drain on the organization's resources—constitutes far more than simply a setback to the organization's abstract social interests." *Havens Realty Corp. v. Coleman*, 455 U.S. 363, 379 (1982) (internal marks omitted).

One way an organization can establish standing is by "identifying specific projects that [it] had to put on hold or otherwise curtail in order to respond to the [challenged action]." *Tex. State LULAC v. Elfant*, 52 F.4th 248, 253 (5th Cir. 2022) (internal marks omitted). This is "not a heightening of the *Lujan* standard,[11] but an example of how to satisfy it by pointing to a non-litigation-related expense." *OCA*, 867 F.3d at 612. Plaintiffs "need not identify specific projects that they have placed on hold or otherwise curtailed."[12] *La Unión del Pueblo Entero v. Abbott*, No. 5:21-CV-0844-XR, 2022 WL 3052489, at *31 (W.D. Tex. Aug. 2, 2022). Rather, this is simply the "most secure foundation" to establish organizational standing. 13A Charles Alan Wright & Arthur R. Miller, *Federal Practice and Procedure* § 3531.9.5 (3d ed. 2022). Furthermore, "'[a]t the pleading stage,' we 'liberally' construe allegations of injury." *Bezet v. United States*, 714 Fed. Appx. 336, 339 (5th Cir. 2017) (quoting *Little v. KPMG LLP*, 575 F.3d 533, 540 (5th Cir. 2009)).

Here, Plaintiff medical associations have standing via diversionary injury. Because of FDA's failure to require reporting of all adverse events, Plaintiffs allege FDA's actions have frustrated their ability to educate and inform their member physicians, their patients, and the public on the dangers of chemical abortion drugs. ECF No. 7 at 12. As a result, Plaintiffs attest they have

[11] *See Lujan v. Defs. of Wildlife*, 504 U.S. 555 (1992).

[12] At the hearing, Danco argued *Elfant* held there was no standing where organizations failed to identify specific projects put on hold. ECF No. 136 at 125. This is incorrect. The Fifth Circuit in *Elfant* assumed without deciding the plaintiffs pled an injury-in-fact but held they did not have standing because the causation and redressability elements were not met. *See* 52 F.4th at 255.

diverted valuable resources away from advocacy and educational efforts to compensate for the lack of information. *See* ECF No. 1 at 91. Such diversions expend considerable time, energy, and resources, to the detriment of other priorities and functions and impair Plaintiffs' ability to carry out their educational purpose. *Id.* at 92; *N.A.A.C.P. v. City of Kyle, Tex.*, 626 F.3d 233, 238 (5th Cir. 2010).[13] Similarly, Plaintiffs allege their efforts to respond to FDA's actions have "tak[en] them away from other priorities such as fundraising and membership recruitment and retention." ECF Nos. 1-4 at 6, 1-5 at 11. Consequently, Plaintiffs have re-calibrated their outreach efforts to spend extra time and money educating their members about the dangers of chemical abortion drugs. Combined, these facts are sufficient to confer organizational standing. *See OCA*, 867 F.3d at 612 (finding organizational standing even where the injury "was not large"); *Fowler*, 178 F.3d at 356 (injuries in fact "need not measure more than an 'identifiable trifle'") (internal marks omitted).

3. Plaintiffs' alleged Injuries are Concrete and Redressable

Defendants contend that Plaintiffs' theories of standing "depend upon layer after layer of speculation." ECF No. 28 at 20. But Plaintiffs allege FDA's chemical abortion regimen "caused" intense side effects and significant complications for their patients requiring medical intervention and attention. ECF No. 7 at 13; *see id.* ("The harms that the FDA has wreaked on women and girls have also injured, and will continue to injure, Plaintiff doctors and their medical practices."); *id.* at 14 ("The FDA's actions have placed enormous pressure and stress on Plaintiff doctors during these

[13] It is true that Plaintiffs must allege their activities in response to the challenged actions differ from their "routine" activities. *See, e.g.*, *City of Kyle*, 626 F.3d at 238. But Plaintiffs have done so. For example, Plaintiffs argue they conducted independent studies and analyses of available data to the detriment of their advocacy, educational, and recruitment efforts. ECF No. 1-8 at 8. The Fifth Circuit has found diversionary injuries to constitute injuries-in-fact even where it was less clear the plaintiffs diverted from routine activities. *See Ass'n of Cmty. Orgs. for Reform Now v. Fowler*, 178 F.3d 350, 360 (5th Cir. 1999) (injury-in-fact where organization regularly conducted voter registration drives and "expended resources registering voters in low registration areas who would have already been registered" if not for the challenged actions).

emergency situations."); *id.* at 15 ("The FDA has caused Plaintiff doctors to face increased exposure to allegations of malpractice and potential liability, along with higher insurance costs."). In fact, Plaintiffs' declarations list specific events where Plaintiff physicians provided emergency care to women suffering from chemical abortion. *See* ECF Nos. 1-8 at 5–6, 1-9 at 4–9, 1-10 at 6–7, 1-11 at 5–6. And Defendants even concede the existence of adverse events related to chemical abortion drugs. *See* ECF No. 28 at 21. Consequently, Defendants misconstrue Plaintiffs' pleadings and mischaracterize Plaintiffs' evidence as "speculative." It is not.

Past injuries thus distinguish this case from *Clapper v. Amnesty Int'l USA*, where the Supreme Court held a "threatened injury must be certainly impending to constitute injury in fact." 568 U.S. 398, 410 (2013) (quoting *Whitmore v. Arkansas*, 495 U.S. 149, 157–58 (1990)). Were there no past injuries in this case, the alleged future harms are still less attenuated than those in *Clapper*. *See id.* (finding "a highly attenuated chain of" *five* separate possibilities needed to align for the alleged harm to occur); *McCardell v. U.S. Dep't of Hous. & Urb. Dev.*, 794 F.3d 510, 520 (5th Cir. 2015) ("[U]nlike in *Clapper,* where the alleged injury depended on a long and tenuous chain of contingent events, the chain-of-events framework in this case involves fewer steps and no unfounded assumptions.") (internal marks omitted). *See also* ECF No. 1-31 at 10 (roughly eight percent of women who use abortion pills will require surgical abortion); ECF No. 1-14 at 23 (discussing a study in which 18.3 percent of women required surgical intervention after chemical abortion). And as post-*Whitmore* cases have demonstrated, the "certainly impending" standard for an "imminent" injury is not as demanding as it sounds. *See TransUnion*, 141 S. Ct. at 2197 (material risk of future harm can suffice "so long as the risk of harm is sufficiently imminent and substantial"); *Susan B. Anthony List v. Driehaus*, 573 U.S. 149, 158 (2014) ("An allegation of future injury may suffice if the threatened injury is 'certainly impending,' *or* there is a 'substantial

risk' that the harm will occur.") (emphasis added); *Clapper*, 568 U.S. at 414 n.5; *Massachusetts v. E.P.A.*, 549 U.S. 497, 526 n.23 (2007) ("Even a small probability of injury is sufficient . . . provided of course that the relief sought would, if granted, reduce the probability."); *Deanda v. Becerra*, No. 2:20-CV-092-Z, 2022 WL 17572093, at *2 (N.D. Tex. Dec. 8, 2022) (collecting cases).[14]

For similar reasons, Defendants' reliance on *City of Los Angeles v. Lyons* also fails. 461 U.S. 95 (1983). There, the Supreme Court held Lyons did not have standing to seek injunctive relief because "[t]here was no finding that Lyons faced a real and immediate threat of again being illegally choked" by Los Angeles police. *Id.* at 110. The *Lyons* holding "is based on the obvious proposition that a prospective remedy will provide no relief for an injury that is, and likely will remain, entirely in the past." *Am. Postal Workers Union v. Frank*, 968 F.2d 1373, 1376 (1st Cir. 1992). "No such reluctance, however, is warranted here." *Hernandez v. Cremer*, 913 F.2d 230, 234 (5th Cir. 1990). Considering FDA's 2021 decision to permit "mail-in" chemical abortion, many women and girls will consume mifepristone without physician supervision. And in maternity-care "deserts," women may not have ready access to emergency care. In sum, there are fewer safety restrictions for women and girls today than ever before. Plaintiffs have good reasons to believe their alleged injuries will continue in the future, and possibly with greater frequency than in the past.

[14] Defendants' reliance on *Spokeo, Inc. v. Robins* is also unavailing. 578 U.S. 330 (2016). Courts should indeed assess whether the alleged injury to the plaintiff has a "close relationship" to harm "traditionally" recognized as the basis for a lawsuit in American courts. *See TransUnion*, 141 S. Ct. at 2204. But "a plaintiff doesn't need to demonstrate that the level of harm he has suffered would be actionable under a similar, common-law cause of action." *Perez v. McCreary, Veselka, Bragg & Allen, P.C.*, 45 F.4th 816, 822 (5th Cir. 2022). Rather, Plaintiffs only need to show the *type* of harm allegedly suffered "is similar in kind to a type of harm that the common law has recognized as actionable." *Id.*; *see also Campaign Legal Ctr. v. Scott*, 49 F.4th 931, 940 (5th Cir. 2022) (Ho., J, concurring) (evidence of injury required by *TransUnion* is not burdensome). Harm resulting from unsafe drugs is similar to harm actionable under the common law.

Defendants next argue Plaintiffs' theories depend on "unfettered choices made by independent actors not before the courts and whose exercise of broad and legitimate discretion the courts cannot presume either to control or to predict." ECF No. 28 at 20 (quoting *Lujan*, 504 U.S. at 562). "[A] plaintiff must allege personal injury fairly traceable to the defendant's allegedly unlawful conduct and likely to be redressed by the requested relief." *Allen v. Wright*, 468 U.S. 737, 751 (1984), *abrogated on other grounds by Lexmark Int'l, Inc. v. Static Control Components, Inc.*, 572 U.S. 118, 134 (2014); *see also Simon v. E. Ky. Welfare Rts. Org.*, 426 U.S. 26, 41–42 (1976) ("In other words, the 'case or controversy' limitation of Art. III still requires that a federal court act only to redress injury that fairly can be traced to the challenged action of the defendant, and not injury that results from the independent action of some third party not before the court.").

In this case, a favorable decision would likely relieve Plaintiffs of at least some of the injuries allegedly caused by FDA. *See Larson v. Valente*, 456 U.S. 228, 243 n.15 (1982) ("[Plaintiffs] need not show that a favorable decision will relieve [their] *every* injury."); *Duke Power Co. v. Carolina Env't Study Grp., Inc.*, 438 U.S. 59, 74–75 (1978) (a "substantial likelihood" of the requested relief redressing the alleged injury is enough); *Sanchez v. R.G.L.*, 761 F.3d 495, 506 (5th Cir. 2014) (a plaintiff "need only show that a favorable ruling could potentially lessen its injury"); *Texas v. Becerra*, 577 F. Supp. 3d 527, 560 (N.D. Tex. 2021) ("That the plaintiffs have brought forth specific evidence and examples of how they *will* be harmed . . . distinguishes this case from others where a third party's actions *might* have hurt the plaintiff."). And redressability is satisfied even if relief must filter downstream through third parties uncertain to comply with the result, provided the relief would either: (1) remove an obstacle for a nonparty to act in a way favorable to the plaintiff; or (2) influence a nonparty to act in such a way. *See, e.g.*, *Dep't of Com. v. New York*, 139 S. Ct. 2551, 2565–66 (2019) ("[T]hird parties will likely react in

predictable ways."); *Bennett v. Spear*, 520 U.S. 154, 169 (1997) (defendants' actions need not be "the very last step in the chain of causation"); *Larson*, 456 U.S. at 242–44; *NiGen Biotech, L.L.C. v. Paxton*, 804 F.3d 389, 396–98 (5th Cir. 2015). Therefore, Plaintiffs' alleged injuries are fairly traceable to Defendants and redressable by a favorable decision.

4. Plaintiffs are within the "Zone of Interests"

Plaintiffs are also within the zone of interests of the Federal Food, Drug, and Cosmetic Act ("FFDCA") and the Comstock Act. Plaintiffs suing under the APA must assert an interest that is "arguably within the zone of interests to be protected or regulated by the statute that they say was violated." *Texas v. United States*, 809 F.3d 134, 162 (5th Cir. 2015) (internal marks omitted). The zone-of-interests test "is not meant to be especially demanding" and is applied "in keeping with Congress's evident intent when enacting the APA to make agency action presumptively reviewable." *Id.* (internal marks omitted). The zone-of-interests test "looks to the law's substantive provisions to determine what interests (and hence which plaintiffs) are protected." *Simmons v. UBS Fin. Servs., Inc.*, 972 F.3d 664, 669 (5th Cir. 2020). "That interest, at times, may reflect aesthetic, conservational, and recreational as well as economic values." *Ass'n of Data Processing Serv. Orgs., Inc. v. Camp*, 397 U.S. 150, 154 (1970).

A federal court's obligation to hear and decide cases within its jurisdiction is "virtually unflagging." *Lexmark*, 572 U.S. at 126 (internal marks omitted). And "the trend is toward enlargement of the class of people who may protest administrative action." *Camp*, 397 U.S. at 154. No "explicit statutory provision" is necessary to confer standing. *Id.* at 155. "The test forecloses suit only when a plaintiff's interests are so marginally related to or inconsistent with the purposes implicit in the statute that it cannot reasonably be assumed that Congress intended to permit the suit." *Texas v. United States*, 809 F.3d at 162 (internal marks omitted). In other words, "[t]here is

no presumption against judicial review and in favor of administrative absolutism unless that purpose is fairly discernible in the statutory scheme." *Camp*, 397 U.S. at 157 (internal marks omitted); *see also Barlow v. Collins*, 397 U.S. 159, 165 (1970) (courts "must decide if Congress has in express or implied terms precluded judicial review or committed the challenged action entirely to administrative discretion").

Defendants argue that Plaintiffs identify no particular provision of the FFDCA protecting their interests. ECF No. 28 at 26. But Plaintiffs' interests are *not* "marginally related" to the purposes implicit in the FFDCA. The statute's substantive provisions protect the safety of physicians' patients and the integrity of the physician-patient relationship. *See generally* 21 U.S.C. § 355. Furthermore, this Court finds Plaintiffs have third-party standing on behalf of their patients. Plaintiffs' patients are within the zone of interest of the FFDCA because patients seek safe and effective medical procedures.

Likewise, Plaintiffs are within the zone of interests of the Comstock Act. This statute "indicates a national policy of discountenancing abortion as inimical to the national life." *Bours v. United States*, 229 F. 960, 964 (7th Cir. 1915); *see also Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 71 n.19 (1983) (the "thrust" of the Comstock Act was "to prevent the mails from being used to corrupt the public morals"). There is no evidence that Congress "sought to preclude judicial review of administrative rulings" by FDA "as to the legitimate scope of activities" available concerning chemical abortion drugs under these statutes. *Camp*, 397 U.S. at 157. For all the aforementioned reasons, Plaintiffs have standing.

B. Plaintiffs' Claims Are Reviewable

Defendants aver that "[a]ll of Plaintiffs' claims are untimely or unexhausted except their challenge to FDA's December 16, 2021, response to the 2019 citizen petition." ECF No. 28 at 26.

This includes Plaintiffs' challenges to: (1) the 2000 Approval and FDA's 2016 Response to the 2002 Petition challenging that approval; (2) the 2019 Generic Approval; and (3), the April 2021 letter. As for FDA's December 2021 Response to the 2019 Petition, Defendants maintain review is limited to the narrow issues presented in the 2019 Petition — which did not include arguments concerning the Comstock Act. *Id.* at 27–28.[15] The Court disagrees with each of these arguments.

1. FDA "Reopened" its Decision in 2016 and 2021

FDA's final decision on a citizen petition constitutes "final agency action" under the APA. 21 C.F.R. § 10.45(c). Challenges to agency actions have a six-year statute of limitations period. *See* 28 U.S.C. § 2401(a). Therefore, the statute of limitations for challenging the 2000 Approval began running on March 29, 2016 — the date of FDA's denial of the 2002 Petition. Because the 2016 Denial of the 2002 Petition occurred more than six years before Plaintiffs filed this suit, Defendants argue the challenge is untimely. ECF No. 28 at 26. But if "the agency opened the issue up anew, and then reexamined and reaffirmed its prior decision," the agency's second action — rather than the original decision — starts the limitations period. *See Texas v. Biden*, 20 F.4th 928, 951 (5th Cir. 2021), *rev'd in part on other grounds*, 142 S. Ct. 2528 (2022).

The reopening doctrine arises "where an agency conducts a rulemaking or adopts a policy on an issue at one time, and then in a later rulemaking restates the policy or otherwise addresses the issue again without altering the original decision."[16] *Wash. All. of Tech. Workers v. U.S. Dep't of Homeland Sec.*, 892 F.3d 332, 345 (D.C. Cir. 2018); *see also Nat'l Biodiesel Bd. v. EPA*, 843 F.3d 1010, 1017 (D.C. Cir. 2016) ("The reopener doctrine allows an otherwise untimely challenge

[15] The Court refers to the 2000 Approval, the 2016 Changes and denial of the 2002 Petition, and the 2019 Generic Approval collectively as FDA's "Pre-2021 Actions." Similarly, the Court refers to FDA's April 2021 letter and December 2021 Response as FDA's "2021 Actions."

[16] Courts have even applied the doctrine where agencies decide *not* to engage in rulemaking and then revisit and reaffirm that decision. *See Pub. Citizen v. Nuclear Regul. Comm'n*, 901 F.2d 147, 152 (D.C. Cir. 1990).

to proceed where an agency has — either explicitly or implicitly — undertaken to reexamine its former choice.") (internal marks omitted); *CTIA-Wireless Ass'n v. F.C.C.*, 466 F.3d 105, 112 (D.C. Cir. 2006) (agency "reconsidered" policy by reaffirming policy and offering "two new justifications" not found in prior orders).

In the rulemaking context, courts have identified four non-exhaustive factors to apply the doctrine where the agency: (1) proposed to make some change in the rules or policies; (2) called for comment on new or changed provisions, but at the same time; (3) explained the unchanged, republished portions; and (4) responded to at least one comment aimed at the previously decided issue. *Tripoli Rocketry Ass'n, Inc. v. U.S. Bureau of Alcohol, Tobacco & Firearms*, No. 00CV0273(RBW), 2002 WL 33253171, at *6 (D.D.C. June 24, 2002) (internal marks omitted). But a court "cannot stop there" — it "must look to the entire context of the rulemaking including all relevant proposals and reactions of the agency to determine whether an issue was in fact reopened." *Pub. Citizen*, 901 F.2d at 150. For example, an agency can reopen a prior action if it removes restrictions or safeguards related to the first action or affects a "sea change" in the regulatory scheme. *See Sierra Club v. EPA*, 551 F.3d 1019, 1025 (D.C. Cir. 2008); *Nat'l Biodiesel*, 843 F.3d at 1017 (declining to apply doctrine when "the basic regulatory scheme remain[ed] unchanged"); *Pub. Citizen*, 901 F.2d at 152 (agency reopens decision when it reiterates a policy in such a way as to render the policy "subject to renewed challenge on any substantive grounds").

In the adjudication context, an agency need not solicit or respond to comments to reopen a decision because adjudication does not require notice and comment procedures. *See* 5 U.S.C. §§ 553(c), 554. The reopening doctrine has been applied in the adjudication context where an agency undertakes a "serious, substantive reconsideration" of "a prior administrative decision." *Chenault v. McHugh*, 968 F. Supp. 2d 268, 275 (D.D.C. 2013); *see also Battle v. Sec'y U.S. Dep't*

of Navy, 757 Fed. Appx. 172, 175 (3d Cir. 2018) (a petition for reconsideration can restart Section 2401(a)'s limitation period if the agency reopens the action based on a finding of "new evidence" or that the petition reflects some "changed circumstances"); *Peavey v. United States*, 128 F. Supp. 3d 85, 100 (D.D.C. 2015), *aff'd*, No. 15-5290, 2016 WL 4098768 (D.C. Cir. 2016) (reopening in 2011 occurred where agency "elected to conduct a substantive review" of servicemember's 1968 application to correct military records). For formal agency adjudications, even an order stating "only that it is denying reconsideration" is not conclusive if the agency has "altered its original decision." *Sendra Corp. v. Magaw*, 111 F.3d 162, 167 (D.C. Cir. 1997).

The standard for reopening is satisfied here. FDA's requirements for distribution in its 2000 Approval originally included:

- In-person dispensing from the doctor to the patient;
- Secure shipping procedures;
- Tracking system ability;
- Use of authorized distributors and agents; and
- Provision of the drug through direct, confidential physician distribution systems that ensures only qualified physicians will receive the drug for patient dispensing.

See ECF No. 1 at 40. FDA's 2016 Changes to this regulatory scheme included the following alterations:

- Extending the maximum gestational age at which a woman or girl can abort her unborn child from 49 days to 70 days;
- Altering the mifepristone dosage from 600 mg to 200 mg, the misoprostol dosage from 400 mcg to 800 mcg, and misoprostol administration from oral to buccal;
- Eliminating the requirement that administration of misoprostol occur in-clinic;
- Broadening the window for misoprostol administration to include a range of 24–48 hours after taking mifepristone, instead of 48 hours afterward;

- Adding a repeat 800 mcg buccal dose of misoprostol in the event of incomplete chemical abortion;
- Removing the requirement for an in-person follow-up examination after an abortion;
- Allowing "healthcare providers" other than physicians to dispense and administer the chemical abortion drugs; and
- Eliminating the requirement for prescribers to report all non-fatal serious adverse events from chemical abortion drugs.

Id. at 53–54. And in 2021, FDA removed the "in-person dispensing requirement" and signaled that it will soon allow pharmacies to dispense chemical abortion drugs. *Id.* at 68. Plaintiffs warn that without this requirement, "there is a dramatically reduced chance that the prescriber can confirm pregnancy and gestational age, discover ectopic pregnancies, and identify a victim of abuse or human trafficking being coerced into having a chemical abortion." ECF No. 120 at 19.

FDA's 2016 and 2021 Changes thus significantly departed from the agency's original approval of the abortion regimen. FDA repeatedly altered its original decision by removing safeguards and changing the regulatory scheme for chemical abortion drugs. *Sierra Club*, 551 F.3d at 1025; *Nat'l Biodiesel*, 843 F.3d at 1017. Additionally, FDA's response to the 2019 Petition *explicitly* states FDA "undertook a *full review* of the Mifepristone REMS Program" in 2021. ECF No. 1-44 at 7 (emphasis added);[17] *see also Peavey*, 128 F. Supp. 3d at 100–02 (agency reopened decision by conducting "thorough review" of the merits, even where the order did not state it was a "reconsideration" and did not reference prior decision). And FDA even granted the 2019 Petition in part. ECF No. 1-44 at 3. A "full review" of a REMS for a drug with known serious risks necessarily considers the possibility that a drug is too dangerous to be on the market, any mitigation

[17] *See also Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation*, FDA (Jan. 4, 2023), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation (describing the 2021 review as "comprehensive").

strategy notwithstanding. FDA has the authority to withdraw an approved drug application on this basis. *See* 21 U.S.C. § 355(e). Because the agency reaffirmed its prior actions after undertaking a substantive reconsideration of those actions, the limitations period for those actions starts in 2021. *See Pub. Citizen*, 901 F.2d at 152 (an agency reconsidering and reaffirming original policy "necessarily raises the lawfulness of the original policy, for agencies have an everpresent duty to insure that their actions are lawful").[18]

Alternatively, the Court finds Plaintiffs' claims are not time-barred under the equitable tolling doctrine. *See United States v. Patterson*, 211 F.3d 927, 931 (5th Cir. 2000) (courts "must be cautious not to apply the statute of limitations too harshly"); *P & V Enters. v. U.S. Army Corps of Engr's*, 466 F. Supp. 2d 134, 149 (D.D.C. 2006), *aff'd,* 516 F.3d 1021 (D.C. Cir. 2008) (a "rebuttable presumption of equitable tolling" applies to lawsuits governed by the six-year limitations period of Section 2401(a)); *Bornholdt v. Brady*, 869 F.2d 57, 64 (2d Cir. 1989) ("The existence of § 2401 as a catchall provision . . . does not necessarily mean that Congress intended the six-year period to be applied whenever a substantive statute does not specify a limitations period."). "[A] litigant is entitled to equitable tolling of a statute of limitations only if the litigant establishes two elements: (1) that he has been pursuing his rights diligently, and (2) that some extraordinary circumstance stood in his way and prevented timely filing." *Menominee Indian Tribe of Wis. v. United States*, 577 U.S. 250, 255 (2016) (internal marks omitted); *see also Holland v. Florida*, 560 U.S. 631, 650 (2010) ("The flexibility inherent in equitable procedure enables courts

[18] To date, it is unclear whether the reopening doctrine has been applied in the precise context of FDA's approval of an NDA. However, much of the rationale courts have applied in both the rulemaking and adjudication context applies here. And the Court is unaware of any legal principle that would preclude the doctrine from being applied to these facts. Assuming *arguendo* Plaintiffs' allegations are true, a contrary holding would mean there is *no* judicial remedy to FDA's insistence on keeping an unsafe drug on the market, so long as enough time has passed.

to meet new situations that demand equitable intervention, and to accord all the relief necessary to correct particular injustices.") (cleaned up).

Equitable tolling is appropriate here in large part because of FDA's unreasonable delay in responding to Plaintiff's 2002 and 2019 Petitions. *See WildEarth Guardians v. U.S. Dep't of Just.*, 181 F. Supp. 3d 651, 670 (D. Ariz. 2015) (it is "grossly inappropriate" to apply a statute of limitations where the agency unreasonably delayed a claim because the agency "could immunize its allegedly unreasonable delay from judicial review simply by extending that delay for six years") (internal marks omitted). It took FDA 13 years, 7 months, and 9 days to respond to the 2002 Petition. FDA then moved the goalposts by substantially changing the regulatory scheme on the *same day* it issued its Response. And it took FDA 2 years, 8 months, and 17 days to respond to the 2019 Petition which challenged those changes. Thus, in the 20 years between the 2002 Petition and the filing of this suit, Plaintiffs were waiting on FDA for over 16 of those years. *See Hill Dermaceuticals, Inc. v. U.S. Food & Drug Admin.*, 524 F. Supp. 2d 5, 9 (D.D.C. 2007) ("Once citizen petitions are submitted, the FDA Commissioner is required to respond in one of three manners 'within 180 days of receipt of the petition.'") (quoting 21 C.F.R. § 10.30(e)(2)).[19]

Additionally, statutes of limitations "are primarily designed to assure fairness to defendants," and "to promote justice by preventing surprises through the revival of claims that have been allowed to slumber until evidence is lost, memories have faded, and witnesses have disappeared." *Clymore v. United States*, 217 F.3d 370, 376 (5th Cir. 2000), *as corrected on reh'g* (Aug. 24, 2000) (internal marks omitted). But it "has not been argued, and cannot seriously be, that the government was unfairly surprised" when Plaintiffs filed this suit. *Id.* Plaintiffs have been

[19] Incidentally, the delayed FDA Response is extreme but not unprecedented. *See, e.g.*, *Bayer HealthCare, LLC v. U.S. Food & Drug Admin.*, 942 F. Supp. 2d 17, 22 (D.D.C. 2013) (FDA had yet to respond to a 2006 petition when it approved a related ANDA in 2013).

reasonably diligent in pursuing their claims. *See, e.g.*, ECF No. 1-4 at 6 (after years of waiting for FDA to respond to the Petition, Plaintiff "called upon" FDA to issue a response in 2005 and again in 2015). And the public interest in this case militates toward resolving Plaintiffs' claims on the merits. Accordingly, Plaintiffs' challenges to FDA's Pre-2021 Actions concerning chemical abortion drugs are not time-barred.

2. FDA's April 2021 Decision on In-Person Dispensing Requirements is not "Committed to Agency Discretion by Law"

Defendants also argue any challenge to FDA's decision regarding the in-person dispensing requirement is foreclosed under *Heckler v. Chaney*, 470 U.S. 821, 832 (1985). ECF No. 28 at 30. In *Heckler*, the Supreme Court held that FDA's decision not to recommend civil or criminal enforcement action to prevent violations of the FFDCA was "committed to agency discretion by law." 470 U.S. at 837–38; *see also Texas v. Biden*, 20 F.4th at 982 ("In other words, a litigant may not waltz into court, point his finger, and demand an agency investigate (or sue, or otherwise enforce against) 'that person over there.'"). "[T]he Supreme Court and the Fifth Circuit have consistently read *Heckler* as sheltering one-off nonenforcement decisions rather than decisions to suspend entire statutes." *Texas v. Biden*, 20 F.4th at 983. The "committed to agency discretion by law" exception to judicial review is a "very narrow exception" that applies *only* where "statutes are drawn in such broad terms that in a given case there is no law to apply." *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 410 (1971), *overruled on other grounds by Califano v. Sanders*, 430 U.S. 99 (1977).

That is not the case here. The Secretary has the authority to determine that drugs with "known serious risks" may be dispensed "only in certain health care settings, such as hospitals." *See* 21 U.S.C. § 355-1(f)(3)(C); *Gomperts v. Azar*, No. 1:19-CV-00345-DCN, 2020 WL 3963864, at *1 (D. Idaho July 13, 2020) ("[T]hese restrictions mandate that Mifeprex be dispensed only in

certain healthcare settings").[20] The statute also provides other "elements to assure safe use" of dangerous drugs. 21 U.S.C. § 355-1(f)(1), (3). The Secretary must publicly explain "how such elements will mitigate the observed safety risk." 21 U.S.C. § 355-1(f)(2). The Secretary must also consider whether the elements would "be unduly burdensome on patient access to the drug" and must "minimize the burden on the health care delivery system." *Id.* Additionally, the elements "shall include [one] or more goals to mitigate a specific serious risk listed in the labeling of the drug." 21 U.S.C. § 355-1(f)(3). And as the Court will later explain, federal law prohibits the mailing of chemical abortion drugs. Thus, unlike in *Heckler*, there *is* "law to apply" to FDA's decision. *See Texas v. Biden*, 20 F.4th at 982 ("[T]he executive *cannot* look at a statute, recognize that the statute is telling it to enforce the law in a particular way or against a particular entity, and tell Congress to pound sand."). And even if Defendants have significant discretion in how they administer Section 355-1, that does not mean *all* related actions are immune to judicial review under Section 701(a)(2) of the APA.

In sum, Defendants cannot shield their decisions from judicial review merely by characterizing the challenged action as exercising "enforcement discretion." ECF No. 28 at 15; *see also Texas v. Biden*, 20 F.4th at 987 ("The Government is still engaged in enforcement — even if it chooses to do so in a way that ignores the statute. That's obviously not nonenforcement."); *id.* at 985 ("*Heckler* cannot apply to agency actions that qualify as rules under 5 U.S.C. § 551(4)."); *Heckler*, 470 U.S. at 833 n.4 (a decision to consciously and expressly adopt a general policy that is "so extreme as to amount to *abdication* of its statutory responsibilities" is not "committed to agency discretion") (emphasis added). Furthermore, the suggestion that FDA has full discretion

[20] *See also Frequently Asked Questions (FAQS) about REMS*, FDA (Jan. 26, 2018), https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/frequently-asked-questions-faqs-about-rems ("A REMS is required to ensure the drug is administered only in a health care facility with personnel trained to manage severe allergic reactions and immediate access to necessary treatments and equipment to managing such events.").

under Section 355-1 to not require *any* REMS for dangerous drugs would likely present nondelegation problems even under a modest view of that doctrine. *See, e.g.*, *Gundy v. United States*, 139 S. Ct. 2116, 2123 (2019). So too the notion that FDA could exercise its non-enforcement discretion in violation of other federal laws. Therefore, FDA's decision to not enforce the in-person dispensing requirement is reviewable because the decision is not committed to agency discretion by law.

3. Plaintiffs' Failure to Exhaust Certain Claims is Excusable

Plaintiffs allege FDA's 2021 Decision to dispense mifepristone through the mail did not acknowledge or address federal criminal laws that "expressly prohibit[] such downstream distribution." ECF No. 7 at 26. Defendants maintain Plaintiffs' argument is unexhausted because they failed to present it at any stage of any administrative proceeding. ECF No. 28 at 38. Similarly, Plaintiffs have not exhausted their challenge to FDA's approval of the supplemental NDA for generic mifepristone. *Id*. at 26. These failures to exhaust claims do not preclude judicial review.

"The general rule of nonreviewability is not absolute." *Myron v. Martin*, 670 F.2d 49, 52 (5th Cir. 1982). To begin, exhaustion is not required where the agency action is "in excess of" the agency's authority. *Id.* And a court will review for the first time "a particular challenge to an agency's decision which was not raised during the agency proceedings" where the agency action is "likely to result in individual injustice" or is "contrary to an important public policy extending beyond the rights of the individual litigants." *Id.*; *see also Mathews v. Eldridge*, 424 U.S. 319, 330 (1976) ("[C]ases may arise where a claimant's interest in having a particular issue resolved promptly is so great that deference to the agency's judgment is inappropriate."); *Abbott Laboratories v. Gardner*, 387 U.S. 136, 149 (1967) (injunctive remedies applied to administrative determinations should evaluate "both the fitness of the issues for judicial decision and the hardship

to the parties of withholding court consideration"); *Dawson Farms, LLC v. Farm Serv. Agency*, 504 F.3d 592, 606 (5th Cir. 2007) (exhaustion may be excused when "irreparable injury will result absent immediate judicial review"); *Bd. of Pub. Instruction of Taylor Cnty., Fla. v. Finch*, 414 F.2d 1068, 1072 (5th Cir. 1969) (exceptional circumstances include "where injustice might otherwise result").

Courts have also excused a claimant's failure to exhaust administrative remedies where exhaustion "would be futile because the administrative agency will clearly reject the claim." *Gulf Restoration Network v. Salazar*, 683 F.3d 158, 176 (5th Cir. 2012) (internal marks omitted); *see also Oregon Nat. Desert Ass'n v. McDaniel*, 751 F. Supp. 2d 1151, 1159 (D. Or. 2011) (exceptional circumstances include evidence of administrative bias). Additionally, courts will consider any issue that was "raised with sufficient clarity to allow the decision maker to understand and rule on the issue raised, whether the issue was considered sua sponte by the agency or was raised by someone other than the petitioning party." *Pac. Choice Seafood Co. v. Ross*, 976 F.3d 932, 942 (9th Cir. 2020). In short, "there is no bright-line standard as to when this requirement has been met." *Nat'l Parks & Conservation Ass'n v. Bureau of Land Mgmt.*, 606 F.3d 1058, 1065 (9th Cir. 2010). Finally, "[a]dministrative remedies that are inadequate need not be exhausted." *Coit Indep. Joint Venture v. Fed. Sav. & Loan Ins. Corp.*, 489 U.S. 561, 587 (1989) (a lack of reasonable time limits in the claims procedure renders the procedure inadequate).

a. Contrary to Public Policy

Judicial review of Plaintiffs' unexhausted claims is appropriate for several reasons. First, Defendants' alleged violation of the Comstock Act would be "contrary to an important public policy." *Myron*, 670 F.2d at 52. As a case Defendants rely upon explains, the word "abortion" in the statute "indicates a national policy of discountenancing abortion as inimical to the national

life." *See Bours*, 229 F. at 964; ECF No. 28-1 at 206. And twenty-two states filed an amicus brief arguing FDA's decision to permit mail-in chemical abortion harms the public interest by undermining states' ability to enforce laws regulating abortion.[21] ECF No. 100 at 17.

b. Individual Injustice and Irreparable Injury

Second, the agency's actions are "likely to result in individual injustice" or cause "irreparable injury." *Myron*, 670 F.2d at 52; *Dawson*, 504 F.3d at 606. Plaintiffs allege "many intense side effects" and "significant complications requiring medical attention" resulting from Defendants' actions.[22] ECF No. 7 at 13. Many women also experience intense psychological trauma and post-traumatic stress from excessive bleeding and from seeing the remains of their aborted children. *See* ECF No. 96 at 25–29; Pauline Slade et al., *Termination of pregnancy: Patient's perception of care*, J. OF FAMILY PLANNING & REPRODUCTIVE HEALTH CARE Vol. 27, No. 2, 72–77 (2001) ("Seeing the foetus, in general, appears to be a difficult aspect of the medical termination process which can be distressing, bring home the reality of the event and may influence later emotional adaptation."). Parenthetically, said "individual justice" and "irreparable injury" analysis also arguably applies to the unborn humans extinguished by mifepristone — especially in

[21] *See* David S. Cohen et al., *Abortion Pills*, 76 STAN. L. REV. 1, 9 (forthcoming 2024) ("Despite state laws, mailed medication abortion can cross borders in ways that undermine state laws . . . A new organization, Mayday Health, for example, focuses on those who live in states with abortion bans, giving users step-by-step instructions on how to set up temporary addresses in an abortion permissive state and forward the mail into the banned state.") (internal marks omitted).

[22] At least 4,213 adverse events from chemical abortion drugs have been reported. *See* ECF No. 96 at 12 n.16. But the actual number is likely far higher because non-fatal adverse events are no longer required to be reported, and because more than 60 percent of women and girls' emergency room visits after chemical abortions are miscoded as miscarriages. *See* James Studnicki et al., *A Post Hoc Exploratory Analysis: Induced Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization*, 9 HEALTH SERV. RSCH. MGMT. EPIDEMIOLOGY 1, 1 (2022); *see also* ECF No. 1-8 at 7 (describing Plaintiffs' difficulty in submitting adverse event reports to mifepristone manufacturer Danco). Other data sources such as the Center for Disease Control and Prevention Abortion Surveillance Reports are "profoundly flawed" because state reporting "is voluntary, with many states reporting intermittently and some not at all." Studnicki et al., *supra* note 9, at 2. One Plaintiff physician alleges that when she reported an adverse event to her state's health department, the "report was rejected because the State said it was not a 'true' adverse event because the patient ultimately recovered." ECF No. 1-10 at 7.

the post-*Dobbs* era. *See Dobbs*, 142 S. Ct. at 2261 ("Nothing in the Constitution or in our Nation's legal traditions authorizes the Court to adopt [the] theory of life" that States are *required* "to regard a fetus as lacking even the most basic human right — to live — at least until an arbitrary point in a pregnancy has passed.") (internal marks omitted); Brief of *Amici Curiae* Scholars of Jurisprudence John M. Finnis and Robert P. George in Support of Petitioners, *Dobbs*, 142 S. Ct. 2228 (2022) (arguing unborn humans are constitutional "persons" entitled to equal protection).

c. Administrative Procedures are Inadequate

Third, FDA's combined response time of over sixteen years to Plaintiffs' two petitions shows their procedures have been inadequate. *See Coit*, 489 U.S. at 587; *Bowen v. City of New York*, 476 U.S. 467, 476 (1986) ("[T]he harm imposed by exhaustion would be irreparable."). FDA slow-walked — or rather, *snail*-walked — its response to the 2002 Petition by waiting nearly *fourteen years* to deny the petition. ECF No. 7 at 9. Requiring Plaintiffs to exhaust their administrative remedies may equate to another decade-plus of waiting for the agency to give them the time of day.

d. Exhaustion would be Futile

Alternatively, any attempt by Plaintiffs to challenge Defendants' actions would likely be futile. Even if Plaintiffs did not endure sixteen years of delay, dawdle, and dithering, their efforts would surely "be futile because the administrative agency will clearly reject the claim." *Gulf Restoration Network*, 683 F.3d at 176. "President Biden has emphasized the need to protect access to mifepristone" since the day of the Supreme Court's decision in *Dobbs*.[23] President Biden stated that "protecting reproductive rights is essential to our Nation's health, safety, and

[23] *See FACT SHEET: President Biden to Sign Memorandum on Ensuring Safe Access to Medication Abortion*, THE WHITE HOUSE (Jan. 22, 2023), https://www.whitehouse.gov/briefing-room/statements-releases/2023/01/22/fact-sheet-president-biden-to-sign-presidential-memorandum-on-ensuring-safe-access-to-medication-abortion/.

progress."[24] He also criticized States' efforts to impose restrictions on mifepristone because such efforts "have stoked confusion, sowed fear, and may prevent patients from accessing safe and effective FDA-approved medication."[25] Thus, it is unlikely FDA would reverse course on its "mail-order" abortion regimen. ECF No. 7 at 7. Defendants' position on the Comstock Act in this litigation only confirms that fact. *See* ECF No. 28 at 38 ("Plaintiffs misconstrue the Comstock Act.").[26]

e. The Comstock Act was raised with Sufficient Clarity

Finally, the Comstock Act issue was "raised with sufficient clarity." *Ross*, 976 F.3d at 942. This is because: (1) the 2019 Petition requested FDA to retain the in-person requirement for dispensing of chemical abortion drugs; and (2) the Comstock Act issue was also raised by the United States Postal Service and the Department of Health & Human Services on July 1, 2022, "[i]n the wake of" *Dobbs*.[27] The Office of Legal Counsel specifically mentioned FDA's regimen for chemical abortion drugs when concluding "the mere mailing of such drugs to a particular jurisdiction is an insufficient basis for concluding that the sender intends them to be used unlawfully." OLC Memo at *1. This shows not only that the issue was raised with sufficient clarity, but also the *futility* of raising the issue before the agency. Therefore, Plaintiffs' failure to exhaust their claims does not preclude judicial review.

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[24] *Memorandum on Further Efforts to Protect Access to Reproductive Healthcare Services*, THE WHITE HOUSE (Jan. 22, 2023), https://www.whitehouse.gov/briefing-room/presidential-actions/2023/01/22/memorandum-on-further-efforts-to-protect-access-to-reproductive-healthcare-services/.

[25] *Id.*

[26] The D.C. Circuit has hinted that the futility doctrine is ordinarily predicated on the "worthlessness of an argument before an agency that *has rejected it* in the *past*" rather than the likelihood that "the agency *would reject it* in the *future*." *Tesoro Refin. & Mktg. Co. v. FERC*, 552 F.3d 868, 874 (D.C. Cir. 2009). But in this case, there is no principled distinction between the two scenarios. Defendants do not even pretend the agency might have accepted Plaintiffs' arguments. Other cases may involve uncertainty about *future* agency rejection, but it is not this case.

[27] *See Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortions*, 2022 WL 18273906 (O.L.C. Dec. 23, 2022) ("OLC Memo").

C. Plaintiffs' Challenges to FDA's 2021 Actions Have a Substantial Likelihood of Success on the Merits

"To satisfy the first element of likelihood of success on the merits," Plaintiffs "must present a prima facie case but need not show that [they are] certain to win." *Janvey v. Alguire*, 647 F.3d 585, 595–96 (5th Cir. 2011) (internal marks omitted). Under the APA, courts must "hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," or "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right." 5 U.S.C. § 706(2)(A) & (C).

The Court will first address FDA's 2021 Actions that eliminated the in-person dispensing requirement and announced that FDA would allow abortionists to dispense chemical abortion drugs by mail or mail-order pharmacy. Plaintiffs have a substantial likelihood of success on their claims that these actions violate federal law.

1. The Comstock Act prohibits the Mailing of Chemical Abortion Drugs

The Comstock Act declares "[e]very obscene, lewd, lascivious, indecent, filthy or vile article, matter, thing, device, or substance" to be "nonmailable matter" that "shall not be conveyed in the mails or delivered from any post office or by any letter carrier." 18 U.S.C. § 1461. The next clauses declare nonmailable "[e]very article or thing designed, adapted, or intended for producing abortion, or for any indecent or immoral use; and [e]very article, instrument, substance, drug, medicine, or thing which is advertised or described in a manner calculated to lead another to use or apply it for producing abortion, or for any indecent or immoral purpose." *Id.* Similarly, Section 1462 forbids the use of "any express company or other common carrier" to transport chemical abortion drugs "in interstate or foreign commerce."

Defendants' argument that the Comstock Act does not prohibit the mailing of chemical abortion drugs relies on the "reenactment canon." That is, courts may distill a statute's meaning

when "federal courts of appeals settled upon a consensus view" and "Congress never modified the relevant statutory text to reject or displace this settled construction." ECF No. 28 at 39. This purported "consensus view" is that the Comstock Act does not prohibit the mailing of items designed to produce abortions "where the sender does not intend them to be used unlawfully." *Id.* This argument is unpersuasive for several reasons.

"Congress is presumed to be aware of an administrative or judicial interpretation of a statute and to adopt that interpretation when it re-enacts a statute without change." *Lorillard v. Pons*, 434 U.S. 575, 580 (1978). But "[t]here is an obvious trump to the reenactment argument": "'[w]here the law is plain, subsequent reenactment does not constitute an adoption of a previous administrative construction.'" *Brown v. Gardner*, 513 U.S. 115, 121 (1994) (quoting *Demarest v. Manspeaker*, 498 U.S. 184, 190 (1991)); *see also Milner v. Dep't of Navy*, 562 U.S. 562, 576 (2011) ("[W]e have no warrant to ignore clear statutory language on the ground that other courts have done so."). Additionally, the presumption only applies when the judicial or administrative gloss "represented settled law when Congress reenacted the [language in question]." *Keene Corp. v. United States*, 508 U.S. 200, 212 (1993); *see also Jama v. Immigr. & Customs Enf't*, 543 U.S. 335, 349 (2005) (presumption applies only when the supposed judicial consensus at the time of reenactment was "so broad and unquestioned that we must presume Congress knew of and endorsed it"); *Davis v. United States*, 495 U.S. 472, 482 (1990); *Fed. Deposit Ins. Corp. v. Phila. Gear Corp.*, 476 U.S. 426, 437 (1986); *United States v. Powell*, 379 U.S. 48, 55 n.13 (1964).[28]

[28] *See also* ANTONIN SCALIA & BRYAN A. GARNER, READING LAW: THE INTERPRETATION OF LEGAL TEXTS 325 (2012) ("But how numerous must the lower-court opinions be, or how prominent and long-standing the administrative interpretation, to justify the level of lawyerly reliance that justifies the canon? What about two intermediate-court decisions? (We doubt it — though some cases have relied on just a single intermediate-court decision.) Or seven courts of first instance? (Perhaps.)").

The canon is easily overcome for one simple reason: it is a dubious means of ascertaining congressional intent. "There are plenty of reasons to reenact a statute that have nothing to do with codifying the glosses that courts have already put on the statute." CALEB NELSON, STATUTORY INTERPRETATION 481 (2011). For example, perhaps the original statute contained a "sunset" provision. Maybe Congress wanted to change the statute in some other respects but found it easier to communicate those changes by reenacting a modified version of the complete statute "than by casting each discrete change as an amendment to the existing language." *Id.* at n.14. Or Congress was perhaps conducting "a more general codification or reorganization of the statutes in a particular field, for the sake of making the structure of its statutes easier to follow." *Id.* "Or maybe Congress simply wanted to enact the relevant title of the United States Code into positive law." *Id.* "To the extent that Congress reenacts statutory language for one of those other reasons, members of Congress may well not mean to be expressing any view at all about the glosses that have piled up in the meantime." *Id.*; *see also* HENRY M. HART, JR., & ALBERT M. SACKS, THE LEGAL PROCESS: BASIC PROBLEMS IN THE MAKING AND APPLICATION OF LAW 1367 (William N. Eskridge, Jr., & Philip P. Frickey eds., 1994) (tent. ed. 1958) (criticizing the canon for adding to the costs of the legislative process in counterproductive ways).

Here, the plain text of the Comstock Act controls. *See Bostock v. Clayton Cnty., Ga.*, 140 S. Ct. 1731, 1749 (2020) ("[W]hen the meaning of the statute's terms is plain, our job is at an end."); *Lawson v. FMR LLC*, 571 U.S. 429, 441 (2014) ("Absent any textual qualification, we presume the operative language means what it appears to mean."). The Comstock Act declares "nonmailable" every "article, instrument, substance, drug, medicine, or thing which is advertised or described in a manner calculated to lead another to use it or apply it for producing *abortion*." 18 U.S.C. § 1461 (emphasis added). It is indisputable that chemical abortion drugs are both

"drug[s]" and are "for producing abortion." Therefore, federal criminal law declares they are "nonmailable." *See Texas v. Becerra*, No. 5:22-CV-185-H, 2022 WL 3639525, at *26 n.21 (N.D. Tex. Aug. 23, 2022) ("[F]ederal law bar[s] the importation or delivery of any device or medicine designed to produce an abortion.").

The statute plainly does *not* require intent on the part of the seller that the drugs be used "unlawfully." To be sure, the statute does contain a catch-all provision that prohibits the mailing of such things "for producing abortion, *or for any indecent or immoral purpose*." 18 U.S.C. § 1461 (emphasis added). But "or" is "almost always disjunctive." *Encino Motorcars, LLC v. Navarro*, 138 S. Ct. 1134, 1141 (2018) (internal marks omitted). Additionally, the "or" in Section 1461 is preceded by a comma, further disjoining the list of nonmailable matter. Thus, the Court does not read the "or" as an "and." Similarly, the Act requires that the defendant "knowingly uses the mails for the mailing" of anything declared by the Act "to be nonmailable." 18 U.S.C. § 1461. A defendant could satisfy this *mens rea* requirement by mailing mifepristone and knowing it is for producing abortion. The statute does not require anything more. *See, e.g.*, *United States v. Lamott*, 831 F.3d 1153, 1157 (9th Cir. 2016) (where Congress "intends to legislate a specific intent crime," the statute typically uses the phrase "with the intent to") (internal marks omitted).

Even if the statute were ambiguous, the legislative history also supports this interpretation.[29] *See* H.R. Rep. No. 91-1105, at 2 (1970) ("Existing statutes completely prohibit the importation, interstate transportation, and mailing of contraceptive materials, or the mailing of advertisement or information concerning how or where such contraceptives may be obtained or how conception may be prevented."). Congress unsuccessfully tried to modify Section 1461 to

[29] This Court reviews the legislative history as mere evidence of the ordinary public meaning of the current statutory language. *See* ANTONIN SCALIA, A MATTER OF INTERPRETATION 17 (1997) ("It is the *law* that governs, not the intent of the lawgiver . . . Men may intend what they will; but it is only the laws that they enact which bind us.").

prohibit mailing drugs "intended by the offender . . . to be used to produce an *illegal* abortion." *See* REP. OF THE SUBCOMM. ON CRIM. JUST., 95TH CONG., REP. ON RECODIFICATION OF FED. CRIM. LAW 40 (Comm. Print 1978) (emphasis added); *Bostock*, 140 S. Ct. at 1824 (Kavanaugh, J., dissenting) ("In the face of the unsuccessful legislative efforts . . . judges may not rewrite the law simply because of their own policy views.").[30] In fact, the House Subcommittee Report on the proposed amendment acknowledged the plain meaning of the statute: "[U]nder current law, the offender commits an offense whenever he 'knowingly' mails any of the designated abortion materials," and the proposed amendment would "require proof that the offender *specifically intended* that the mailed materials be used to produce an illegal abortion."[31] If Congress believed the statute *already* contained the "intentionality" requirement gloss in prior reenactments, there is little reason why Congress would amend the provision to *include* that requirement.

Defendants aver Plaintiffs' interpretation of the Comstock Act is foreclosed by the Food and Drug Administration Amendments Act of 2007 ("FDAAA") for one reason: "Congress was well aware that it was directing mifepristone's preexisting distribution scheme to continue" in enacting the FDAAA. ECF No. 28 at 40. But neither "critics [of FDA's 2000 Approval of mifepristone] nor anyone else in the congressional debate mentioned the Comstock Act." OLC Memo at *7 n.18; *see also In re Lively*, 717 F.3d 406, 410 (5th Cir. 2013) ("Repeals by implication are disfavored and will not be presumed unless the legislature's intent is 'clear and manifest.'") (internal marks omitted). Because the Comstock Act is not even implicitly mentioned

[30] *Bostock*'s majority opinion warns that "speculation about why a later Congress declined to adopt new legislation offers a 'particularly dangerous' basis on which to rest an interpretation of an existing law a different and earlier Congress did adopt." 140 S. Ct. at 1747. But the opinion does not suggest judges can "rewrite the law." Instead, *Bostock*'s stated rationale was that the disputed term was implicit in the statutory text all along. No such "textualist" analysis could plausibly justify Defendants' interpretation of the Comstock Act, and Defendants offer none.

[31] REP. OF THE SUBCOMM. ON CRIM. JUST., 95TH CONG., REP. ON RECODIFICATION OF FED. CRIM. LAW 40 (Comm. Print 1978) (emphasis added).

in the FDAAA's enactment, there is no repeal by implication. And in any case, Defendants' arguments based on legislative history cannot overcome clear statutory text.

Consequently, reenactment of the Comstock Act does not constitute an adoption of prior constructions because "the law is plain." *Brown*, 513 U.S. at 121 (1994). Even if that were not the case, the reenactment canon does not apply here because the relevant judicial glosses do not represent a "broad and unquestioned" consensus. *Jama*, 543 U.S. at 349. Defendants rely heavily on the OLC Memo that purports to establish this "consensus." But none of the cases cited in the OLC Memo support the view that the Comstock Act bars the mailing of abortion drugs only when the sender has the specific intent that the drugs be used unlawfully.

On the contrary, the Seventh Circuit reasoned that the word "abortion" in the context of the Act indicates "a national policy of discountenancing abortion as inimical to the national life." *Bours*, 229 F. at 964. *Bours* further declared "it is immaterial what the local statutory definition of abortion is, what acts of abortion are included, or what excluded." *Id.* Similarly, the Sixth Circuit's decision in *Davis v. United States* only suggests that legitimate uses of drugs should not fall within the scope of the statute "merely because they are capable of illegal uses." 62 F.2d 473, 474 (6th Cir. 1933). In other words, the *Davis* holding reflects the position that *legitimate* uses — uses beyond the purposes the statute condemns — should be excluded from the scope of the statute, *not* that whatever uses are *lawful under state law* should be. ECF No. 114 at 10. Likewise, the Second Circuit interpreted the statute to embrace articles the 1873 Congress "would have denounced as immoral if it had understood all the conditions under which they were to be used." *United States v. One Package*, 86 F.2d 737, 739 (2d Cir. 1936). The court further observed that "[t]he word 'unlawful' would make this clear as to articles for producing abortion." *Id.*; *see also* James S. Witherspoon, *Reexamining Roe: Nineteenth-Century Abortion Statutes and the Fourteenth*

Amendment, 17 ST. MARY'S L.J. 29, 33 (1985) (explaining that thirty of thirty-seven states had statutory abortion prohibitions in 1868 — just five years before Congress enacted the Comstock Act).

Defendants maintain "the legality of the agency actions needs to be judged at the time of the decision, all of which occurred when *Roe* and *Casey* were still good law." ECF No. 136 at 109. Even assuming that is true in all cases, *Roe* did not prohibit *all* restrictions on abortions. And it is not obvious that enforcement of the Comstock Act post-*Casey* would have necessarily run afoul of *Casey*'s "arbitrary 'undue burden' test." *Dobbs*, 142 S. Ct. at 2266. Therefore, there is no reason why the Act should not have at least been considered. In any case, the Comstock Act plainly forecloses mail-order abortion in the present, and Defendants have stated no present or future intention of complying with the law. Defendants cannot immunize the illegality of their actions by pointing to a small window in the past where those actions might have been legal.

In sum, the reenactment canon is inapplicable here because the law is plain. Even if that were not true, the cases relied on in the OLC Memo do not support Defendants' interpretation. And even if they did, a small handful of cases cannot constitute the "broad and unquestioned" consensus required under the reenactment canon. Therefore, Plaintiffs have a substantial likelihood of prevailing on their claim that Defendants' decision to allow the dispensing of chemical abortion drugs through mail violates unambiguous federal criminal law.

2. FDA's 2021 Actions violate the Administrative Procedure Act

Because FDA's 2021 Actions violate the Comstock Act, they are "otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). Additionally, the actions were likely "arbitrary and capricious." *Id.* FDA relied on FDA Adverse Event Reporting System data despite the agency's 2016 decision to eliminate the requirement for abortionists to report non-fatal "adverse events."

ECF No. 7 at 25. Defendants maintain that "Plaintiffs offer no explanation for why it was impermissible to rely on the reported data." ECF No. 28 at 33. The explanation should be obvious — it is circular and self-serving to practically eliminate an "adverse event" reporting requirement and then point to a low number of "adverse events" as a justification for removing even *more* restrictions than were already omitted in 2000 and 2016. In other words, it is a predetermined conclusion in search of non-data — a database designed to produce a null set. But even if FDA's explanation were well-reasoned, the actions would still run afoul of the Comstock Act and therefore violate the APA.

D. Plaintiffs' Challenges to FDA's Pre-2021 Actions Have a Substantial Likelihood of Success on the Merits

1. FDA's 2000 Approval violated Subpart H

In 1992, FDA issued regulations "needed to assure safe use" of *new* drugs designed to treat life-threatening diseases like HIV and cancer. *See* 57 Fed. Reg. 58,942, 58,958 (Dec. 11, 1992) (codified at 21 C.F.R. § 314.520). Subpart H — titled "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" — applies to drugs that satisfy two requirements. First, the drug must have been "studied for [its] safety and effectiveness in treating serious or life-threatening illnesses." 21 C.F.R. § 314.500. And second, the drug must "provide [a] meaningful therapeutic benefit to patients over existing treatments." *Id.* "These rules were promulgated by FDA . . . as part of an attempt to correct perceived deficiencies in FDA's approval process made apparent by the need to quickly develop drugs for HIV/AIDS patients." ECF No. 1-13 at 20.

"When FDA originally approved Mifeprex, the agency relied upon Subpart H to place certain restrictions on the manufacturer's distribution of the drug product to assure its safe use." ECF No. 28 at 14; *see also* ECF No. 1-13 at 9 (the American Medical Association explained that "[Mifepristone] poses a severe risk to patients unless the drug is administered as part of a complete

treatment plan under the supervision of a physician"). Thus, to satisfy Subpart H, FDA deemed pregnancy a "serious or life-threatening illness[]" and concluded that mifepristone "provide[d] [a] meaningful therapeutic benefit to patients over existing treatments." *See* 21 C.F.R. §§ 314.500; 314.560. FDA was wrong on both counts.

a. Pregnancy is not an "Illness"

Pregnancy is a normal physiological state most women experience one or more times during their childbearing years — a natural process essential to perpetuating human life. Defendants even admit pregnancy is not an "illness." FDA claims the Final Rule explained Subpart H was available for serious or life-threatening "conditions," whether or not they were understood colloquially to be "illnesses." ECF No. 28 at 36. But the Final Rule says no such thing. "One comment asserted that neither depression nor psychosis is a disease, nor is either one serious or life-threatening." 57 Fed. Reg. 58,946. FDA responded to the comment that "signs of these diseases are readily studied" and that its reference to depression and psychosis "was intended to give examples of conditions or diseases that can be serious for certain populations or in some or all of their phases." *Id.* In other words, FDA's response to this comment was *not* that depression and psychosis qualify because they are "conditions" even though they are not colloquially understood as "illnesses." Rather, FDA simply disagreed with the comment's characterization of these conditions and explained that they *were* examples of "diseases" that can be "serious." Nothing in the Final Rule supports the interpretation that pregnancy is a serious or life-threatening illness.

FDA's 2016 Denial of the 2002 Petition is similarly unpersuasive. For example, FDA noted that approximately fifty percent of pregnancies in the United States are unintended and that unintended pregnancies may cause depression and anxiety. ECF No. 1-28 at 5. But categorizing

complications or negative psychological experiences arising *from* pregnancy as "illnesses" is materially different than classifying pregnancy *itself* as a serious or life-threatening illness *per se*. Tellingly, FDA never explains how or why a "condition" would *not* qualify as a "serious or life-threatening illness." Suppose that a woman experiences depression because of lower back pain that inhibits her mobility. Under FDA's reading, a new drug used to treat lower back pain — which can cause depression, just like unplanned pregnancy — could obtain accelerated approval under Subpart H.

Defendants cite zero cases reading Subpart H like FDA reads Subpart H. On the contrary, courts have read "serious or life-threatening illnesses" to mean what it says. *See, e.g.*, *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 182 (E.D.N.Y. 2013) ("Whether an illness is 'serious or life-threatening' 'is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.'") (quoting 57 Fed. Reg. at 13235). The preamble to the final rule also clarified the terms "would be used as FDA has defined them in the past." 57 Fed. Reg. at 13235.

Likewise, the Final Rule expressly stated this nomenclature "is the same as FDA defined and used the terms" in two rulemakings: the first in 1987; the second in 1988. 57 Fed. Reg. at 58,945. In the 1988 rulemaking, FDA defined "life-threatening" to include *diseases or conditions* "where the likelihood of death is high unless the course of the disease is interrupted (*e.g.*, AIDS and cancer), as well as diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival (*e.g.*, increased survival in persons who have had a stroke or heart attack)." *See* 53 Fed. Reg. at 41517; *id.* at 41516 (referencing "AIDS, cancer, Parkinson's disease, and other serious conditions"); *CSX Transp., Inc. v. Ala. Dep't of Revenue*, 562 U.S. 277, 294 (2011) (the canon of *ejusdem generis* "limits general terms that follow specific ones to matters

similar to those specified") (internal marks omitted). Therefore, "diseases" and "conditions" are used interchangeably, and even "conditions" must be "serious" or "life-threatening" as defined.

Food and Drug scholars have understood Subpart H's scope the same way. *See, e.g.*, Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 FOOD & DRUG L.J. 295, 323 (2006) (Subpart H "extend[s] only to drugs and biological products that target[] 'serious or life-threatening illnesses' and offer[] a 'meaningful' benefit over existing treatments"). Even the Population Council argued to FDA that "the imposition of Subpart H is unlawful" because "[t]he plain meaning of these terms does not comprehend normal, everyday occurrences such as pregnancy and unwanted pregnancy." ECF No. 1-14 at 21. This reading is also consistent with the fact that aside from mifepristone, FDA had approved fewer than forty NDAs under Subpart H by early 2002. *See id.* at 20. And of those *other* approvals, twenty were for the treatment of HIV and HIV-related diseases, nine were for the treatment of various cancers and their symptoms, four were for severe bacterial infections, one was for chronic hypertension, and one was for leprosy. *Id.* "One of these things is not like the others, one of these things just doesn't belong." *See Sesame Street*.

b. Defendants are not entitled to Auer *Deference*

Courts sometimes extend *Auer* deference "to agencies' reasonable readings of genuinely ambiguous regulations." *Kisor v. Wilkie*, 139 S. Ct. 2400, 2408 (2019). *Auer* deference is rooted in an "always rebuttable" presumption "that Congress would generally want the agency to play the primary role in resolving regulatory ambiguities." *Id.* at 2412. "*Auer* deference is sometimes appropriate and sometimes not." *Id.* at 2408. "First and foremost, a court should not afford *Auer* deference unless the regulation is genuinely ambiguous." *Id.* at 2415. "And before concluding that a rule is genuinely ambiguous, a court must exhaust all the traditional tools of construction." *Id.*

(internal marks omitted). "That means a court cannot wave the ambiguity flag just because it found the regulation impenetrable on first read." *Id.* If genuine ambiguity remains, the agency's reading must still be "reasonable." *Id.* And even if the regulation is genuinely ambiguous, the agency's interpretation "must in some way implicate its substantive expertise." *Id.* at 2417. Finally, an agency's reading of a rule must reflect "fair and considered judgment" to receive *Auer* deference. *Id.* (internal marks omitted).

Here, *Auer* deference is not appropriate because "the language of [the] regulation is plain and unambiguous." *McCann v. Unum Provident*, 907 F.3d 130, 144 (3d Cir. 2018). As explained, FDA's definitions in prior rulemakings foreclose its interpretation of Subpart H. If there is any ambiguity in "serious or life-threatening illnesses," the ordinary meaning principle resolves that ambiguity. *See Bostock*, 140 S. Ct. at 1825 (Kavanaugh, J, dissenting) ("The ordinary meaning principle is longstanding and well settled."). "[C]ommon parlance matters in assessing the ordinary meaning" of a statute or regulation "because courts heed how most people would have understood the text." *Id.* at 1828 (internal marks omitted). The word "illness" refers to "poor health; sickness," or "a specific sickness or disease, or an instance of such."[32] Merriam-Webster invokes the definition for "sickness" — "an unhealthy condition of body or mind."[33] Likewise, a Wikipedia search for "illness" re-directs to the entry for "Disease," which is defined as "a particular *abnormal* condition that negatively affects the structure or function of all or part of an organism, and that is not immediately due to any external injury."[34] Pregnancy, on the other

[32] *Illness*, Dictionary.com, https://www.dictionary.com/browse/illness (last visited Mar. 22, 2023); *see also Bostock*,140 S. Ct. at 1766 (Alito, J, dissenting) ("Dictionary definitions are valuable because they are evidence of what people at the time of a statute's enactment would have understood its words to mean.").

[33] *Illness*, Merriam-Webster.com, https://www.merriam-webster.com/dictionary/illness (last visited Mar. 22, 2023).

[34] *Disease*, Wikipedia, https://en.wikipedia.org/wiki/Disease (emphasis added) (last visited Mar. 22, 2023).

hand, is defined as "the time during which one or more offspring develops (gestates) inside a woman's uterus (womb)."[35]

Most readers would not define pregnancy to be a serious or life-threatening illness. Even FDA does not earnestly defend that position. True, complications can arise during pregnancy, and said complications *can* be serious or life-threatening. But that does not make pregnancy *itself* an illness. *See* ECF No 1-13 at 21. And even if the regulation were genuinely ambiguous after exhausting all traditional tools of statutory construction, Defendants' interpretation: (1) is *not* reasonable; (2) does not implicate their substantive expertise; and (3) does not reflect fair and considered judgment. Accordingly, Defendants are not entitled to *Auer* deference on their interpretations of "serious or life-threatening illnesses." By interpreting Subpart H's scope as reaching any state or side effect that can be considered an undefined "condition," Defendants broaden the regulation on accelerated approval of new drugs farther than the text of the regulation would ever suggest. Therefore, FDA's approval of chemical abortion drugs under Subpart H exceeded its authority under the regulation's first requirement.

c. Chemical Abortion Drugs do not provide a "Meaningful Therapeutic Benefit"

FDA also exceeded its authority under the second requirement of Subpart H. In addition to treating a serious or life-threatening illness, chemical abortion drugs must also provide a "meaningful therapeutic benefit" to patients over surgical abortion. 21 C.F.R. § 314.500. As explained, this cannot be the case because chemical abortion drugs do not treat "serious or life-threatening illnesses" — a prerequisite to reaching the second requirement. *Id.* Similarly, chemical abortion drugs cannot be "therapeutic" because the word relates to the treatment or curing of disease.[36] But even putting that aside, chemical abortion drugs do not provide a meaningful

[35] *Pregnancy*, Wikipedia, https://en.wikipedia.org/wiki/Pregnancy (last visited Mar. 22, 2023).
[36] *Therapeutic*, Dictionary.com, https://www.dictionary.com/browse/illness (last visited Mar. 28, 2023).

therapeutic benefit over surgical abortion. *See* 21 C.F.R. § 314.500 (examples include where the benefit is the "ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy"). To the extent surgical abortion can be considered a "therapy," the clinical trials did not compare chemical abortion with surgical abortion to find such a benefit. ECF No. 1 at 44.

Defendants argue just one "meaningful therapeutic benefit": chemical abortion drugs avoided "an invasive surgical procedure and anesthesia in 92 percent of" patients in the trial. ECF No. 28 at 37. But "[b]y defining the 'therapeutic benefit' solely as the avoidance of the current standard of care's delivery mechanism, FDA effectively guarantees that a drug will satisfy this second prong of Subpart H as long as it represents a different method of therapy." ECF No. 1-14 at 22. And even if that *were* a benefit, chemical abortions are over fifty percent more likely than surgical abortion to result in an emergency room visit within thirty days. ECF No. 7 at 21.[37] Consequently, the number of chemical abortion-related emergency room visits increased by over *five hundred percent* between 2002 and 2015. ECF No. 1 at 19.

One study revealed the overall incidence of adverse events is "fourfold higher" in chemical abortions when compared to surgical abortions.[38] Women who underwent chemical abortions also experienced far higher rates of hemorrhaging, incomplete abortion, and unplanned surgical evacuation.[39] Chemical abortion patients "reported significantly higher levels of pain, nausea,

[37] Some studies report that the exact number is *fifty-three* percent. *See* Studnicki et al., *supra* note 22.

[38] *See* Maarit Niinimäki et al., *Immediate Complications After Medical Compared with Surgical Termination of Pregnancy*, 114 OBSTETRICS & GYNECOLOGY 795 (2009). FDA agrees with this study but finds it "not surprising" given that chemical abortion "is associated with longer uterine bleeding." ECF No. 1-44 at 38. *See also* ECF No 1-13 at 15, n.68–72 (collecting studies demonstrating the far higher rates of adverse events in chemical abortion over surgical abortion).

[39] *Id.*

vomiting and diarrhea during the actual abortion than did surgical patients . . . Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients." ECF No 1-13 at 24. And before the approval, an FDA medical officer recognized the "medical regimen had *more* adverse events, particularly bleeding, than did surgical abortion. Failure rates exceeded those for surgical abortion . . . This is a serious potential disadvantage of the medical method." *Id.* at 23 (emphasis added).

Other studies show eighty-three percent of women report that chemical abortion "changed" them — and seventy-seven percent of those women reported a *negative* change.[40] Thirty-eight percent of women reported issues with anxiety, depression, drug abuse, and suicidal thoughts because of the chemical abortion.[41] Bleeding from a chemical abortion, unlike surgical abortion, can last up to several weeks.[42] And the mother seeing the aborted human "appears to be a difficult aspect of the medical termination process which can be distressing, bring home the reality of the event and may influence later emotional adaptation."[43] "For example, one woman was surprised and saddened to see that her aborted baby 'had a head, hands, and legs' with '[d]efined fingers and toes.'" ECF No. 1 at 21. The entire abortion process takes place within the mother's home, without physician oversight, potentially leading to undetected ectopic pregnancies, failure of rH factor incompatibility detection, and misdiagnosis of gestational age — all leading to severe or even fatal

[40] *See* Katherine A. Rafferty & Tessa Longbons, *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives*, 36 HEALTH COMM. 1485, 1485–94 (2021), https://www.tandfonline.com/doi/full/10.1080/10410236.2020.1770507.

[41] *Id.*

[42] *After Mifepristone: When bleeding will start and how long will it last?*, WOMEN ON WEB, https://www.womenonweb.org/en/page/484/when-will-you-start-bleeding-and-howlong-will-it-last. *See also* ECF No. 1-28 at 25 ("Up to 8% of all subjects may experience some type of bleeding for 30 days or more.").

[43] Pauline Slade et al., *Termination of Pregnancy: Patient's Perception of Care*, 27 J. OF FAMILY PLANNING & REPRODUCTIVE HEALTH CARE 72, 76 (2001).

consequences. *See* ECF No. 96 at 15–17. Contrary to popular belief and talking points, the evidence shows chemical abortion is *not* "as easy as taking Advil." *Id.* at 20.

Compelling evidence suggests the statistics provided by FDA on the adverse effects of chemical abortion *understate* the negative impact the chemical abortion regimen has on women and girls. When women seek emergency care after receiving the chemical abortion pills, the abortionist that prescribed the drugs is usually *not* the provider to manage the mother's complications.[44] Consequently, the treating physician may not know the adverse event is due to mifepristone. *Id.* at 13. Studies support this conclusion by finding *over sixty percent* of women and girls' emergency room visits after chemical abortions are miscoded as "miscarriages" rather than adverse effects to mifepristone.[45] Simply put, FDA's data are incomplete and potentially misleading, as are the statistics touted by mifepristone advocates.

Lastly, chemical abortion does not "treat patients unresponsive to, or intolerant of, available therapy." *See* 21 C.F.R. § 314.500. "To the contrary, because 'medical abortion failures should be managed with surgical termination' the option for surgical abortion must be available for any Mifeprex patient." ECF No. 1-14 at 23 (quoting the Mifeprex "Warnings" label). One study showed that 18.3 percent of women required surgical intervention after the chemical abortion regimen failed. *Id.* Hence, "any patient who would be intolerant of surgical abortion, if such a class of patients exists, cannot use the Mifeprex Regimen." *Id.* at 24. On balance, the data reflect little to no benefit over surgical abortion — much less a "meaningful therapeutic" benefit.

[44] Kathi Aultman et al., *Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019*, 36 ISSUES IN LAW & MED., 3–26 (2021).

[45] Studnicki et al., *supra* note 9.

d. Defendants' Misapplication of Subpart H has not been Cured by Congress

Defendants contend "Plaintiffs' arguments about Subpart H have been overtaken by congressional action." ECF No. 28 at 35. In the FDAAA, "Congress specifically directed" that drugs with elements to assure safe use "in effect on the effective date on this Act" would be "deemed to have in effect an approved" REMS. *Id.* (citing Pub. L. No. 110-85, § 909(b)(1)). But the sponsors of such drugs were also required to submit a proposed REMS within 180 days. *See* Pub. L. No. 110-85, § 909(b)(3). Hence, Congress "deemed" preexisting safety requirements to be a sufficient REMS until a *new* REMS was approved. The FDAAA did not affect, however, whether an NDA was properly approved or authorized under Subpart H in the first place. Rather, the FDAAA required that such drugs needed continued restrictions in place to mitigate risks. Implementation of a REMS under the FDAAA does not somehow repeal or supplant the approval process under Subpart H or 21 U.S.C. § 355(d). The FDAAA only eased the regulatory transition from Subpart H to the REMS provision. Simply stated, Congress's *general* reiteration that dangerous drugs should carry a REMS did not codify FDA's *specific* approval of the mifepristone NDA. It did not consider the chemical abortion approval at all.

In sum, Subpart H doubly forecloses FDA's approval of mifepristone. *At most*, FDA might have lawfully approved mifepristone under Subpart H for cases where a pregnant woman's life or health is in danger. But even a limited approval of this sort would still not render pregnancy an "illness." And surgical abortion — a statistically far safer procedure — would still be available to her. But in any case, that is not what FDA did. Instead, FDA manipulated and misconstrued the text of Subpart H to greenlight elective chemical abortions on a wide scale. Therefore, Plaintiffs have a substantial likelihood of prevailing on their claim that Defendants violated Subpart H.

2. FDA's Pre-2021 Actions were Arbitrary and Capricious

Under the FFDCA, a pharmaceutical company seeking to market a new drug must first obtain FDA approval via an NDA. *See* 21 U.S.C. § 355(a), (b). The NDA must include "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d). The trials must "provide an adequate basis for physician labeling." 21 C.F.R. § 312.21(c). In those trials, "the drug is used *the way it would be administered when marketed*."[46] The Secretary must deny the NDA if "he has insufficient information to determine whether such drug is safe for use under such conditions." 21 U.S.C. § 355(d)(4).

Here, the U.S. trials FDA relied upon when approving mifepristone required that: (1) each woman receive an ultrasound to confirm gestational age and exclude an ectopic pregnancy;[47] (2) physicians have experience in performing surgical abortions and admitting privileges at medical facilities that provide emergency care; (3) all patients be within one hour of emergency facilities or the facilities of the principal investigator; and (4) women be monitored for four hours to check for adverse events after taking misoprostol. ECF No. 7 at 23. However, FDA included *none* of these requirements — which were explicitly stated in the clinical trial FDA relied on most — in the 2000 Approval. *Id.* Likewise, FDA's 2016 Changes omitted the requirements of the underlying tests: (1) gestational age confirmed by ultrasounds; (2) participants required to return for clinical assessment; and (3) surgical intervention if necessary. *Id.* at 24.

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[46] *Glossary*, WEILL CORNELL MEDICINE, https://research.weill.cornell.edu/compliance/human-subjects-research/institutional-review-board/glossary-faqs-medical-terms-lay-3 (last visited Mar. 22, 2023) (emphasis added).

[47] The 2016 Denial of the 2002 Petition briefly notes the two French clinical trials did not *require* an ultrasound but instead left the decision to the investigator's discretion. ECF No. 1-28 at 19 n.47. Defendants do not explain how many investigators chose to perform an ultrasound. The higher that number is, the more it supports Plaintiffs' argument. But in any case, the U.S. trial was larger than the two French trials combined and is therefore the more reliable study. *Id.* at 9.

Defendants maintain "there is no legal basis for Plaintiffs' contention that the approved conditions of use of a drug must duplicate the protocol requirements for the clinical trials supporting its approval." ECF No. 28 at 35. But FDA's actions must not be arbitrary and capricious.[48] *See* 5 U.S.C. § 706(2)(A); *United States v. An Article of Device . . . Diapulse*, 768 F.2d 826, 832–33 (7th Cir. 1985) (concluding FDA's denial was not arbitrary and capricious because the proposed labeling did not "specify conditions of use that are similar to those followed in the studies"). "The scope of review under the arbitrary and capricious standard is narrow and a court is not to substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (internal marks omitted). "Nevertheless, the agency must examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Id.* (internal marks omitted); *see also Sw. Elec. Power Co. v. EPA*, 920 F.3d 999, 1013 (5th Cir. 2019) (judicial review of agency action "is not toothless"). Courts must "consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Id.* (internal marks omitted). An agency's action is "arbitrary and capricious" if it "entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Id.* Defendants fail this test.

[48] Plaintiffs also frame what the Court characterized as the "study-match problem" as a statutory violation of the FFDCA. *See* ECF No. 7 at 22. The Court does not read 21 U.S.C. § 355(d) as necessarily *requiring* an exact "match" between trial conditions and the conditions on the approved labeling of a new drug. But Section 355(d) does mandate the Secretary "issue an order refusing to approve the application" if he finds the investigations do not show the drug is safe for use under the suggested conditions in the proposed labeling. FDA made such a finding yet did not deny the Application. *See* ECF No. 1-24 at 6 ("We have concluded that adequate information has not been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for use as recommended."). Thus, even if Defendants could survive "arbitrary and capricious" analysis of the "study-match problem," Defendants still violated Section 355(d) on their own terms.

a. The 2000 Approval

To begin, FDA "entirely failed to consider an important aspect of the problem" by omitting any evaluation of the psychological effects of the drug or an evaluation of the long-term medical consequences of the drug. *State Farm*, 463 U.S. at 43; ECF No. 84 at 12. Considering the intense psychological trauma and post-traumatic stress women often experience from chemical abortion, this failure should not be overlooked or understated. Nor was the drug tested for under-18 girls undergoing reproductive development.[49] But that is not all. Clinical trial protocols in the United States for the 2000 Approval required a transvaginal ultrasound for each patient to accurately date pregnancies and identify ectopic pregnancies. ECF No. 1-28 at 19. But FDA ultimately concluded that "a provider can accurately make such a determination by performing a pelvic examination and obtaining a careful history." *Id.* Thus, FDA determined it was inappropriate "to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy." ECF No. 1-28 at 19. FDA believed "it is reasonable to expect that the women's providers would not have prescribed Mifeprex if a pelvic ultrasound examination had clearly identified an ectopic pregnancy." *Id.* at 20.

FDA thus assumes physicians will ascertain gestational age. But put another way, there is simply *no requirement* that *any* procedure is done to rule out an ectopic pregnancy — which *is* a serious and life-threatening situation. This is arbitrary and capricious. The mere fact that other clinical methods can be used to date pregnancies does not support the view that it should be the

[49] In 1998, FDA issued the "Pediatric Rule," which "mandated that drug manufacturers evaluate the safety and effectiveness of their products on pediatric patients, absent an applicable exception." *Ass'n of Am. Physicians & Surgeons, Inc. v. U.S. Food & Drug Admin.*, 391 F. Supp. 2d 171, 173–74 (D.D.C. 2005). Two years after approving mifepristone, FDA was enjoined from enforcing the Pediatric Rule because it lacked statutory authority in issuing the rule. *See Ass'n of Am. Physicians & Surgeons v. FDA*, 226 F. Supp. 2d 204, 222 (D.D.C. 2002). In response, Congress enacted the Pediatric Research Equity Act of 2003 to codify the Pediatric Rule. *See* 21 U.S.C. § 355c. In the 2000 Approval, FDA clarified that the Mifeprex NDA was covered by the Pediatric Rule. *See* ECF No. 1-26 at 4. However, FDA fully waived the rule's requirements without explanation. ECF No. 1-28 at 30.

provider's decision to decide which method — if any — is used to make this determination. FDA has never denied that an ultrasound is the *most accurate* method to determine gestational age and identify ectopic pregnancies. *See* ECF No. 1-14 at 62. And the fact that other clinical methods can be used does not mean that all such methods are equal in their accuracy and reliability.[50] FDA did rely on a study showing that clinicians rarely underestimate gestational age. ECF No. 1-28 at 19 n.49. But this study does nothing to support FDA's view that a transvaginal ultrasound is not necessary to diagnose ectopic pregnancies. To this point, FDA merely argues that even transvaginal ultrasounds do not *guarantee* an existing ectopic pregnancy will be identified. *Id.* at 19. If that is the case, it does not follow that it should be left to the provider's discretion to employ less reliable methods — or no methods at all.

Correct diagnosis of gestational age and ectopic pregnancies is vital. The error in FDA's judgment is borne out by myriad stories and studies brought to the Court's attention. One woman alleged she did not receive an ultrasound or any other physical examination before receiving chemical abortion drugs from Planned Parenthood. ECF No. 1 at 22. "The abortionist misdated the baby's gestational age as six weeks, resulting in the at-home delivery of a 'lifeless, fully-formed baby in the toilet,' later determined to be around *30-36 weeks old*." *Id.*; *see also Patel v. State*, 60 N.E.3d 1041, 1043 (Ind. Ct. App. 2016) (woman who used chemical abortion drugs "delivered a live baby of approximately twenty-five to thirty weeks gestation who died shortly after birth"). Another woman was given chemical abortion drugs during an ectopic pregnancy because her ultrasound "was not even that of a uterus but was of a bladder."[51] ECF No. 31 at 5.

[50] Studies reflect that women recurrently miscalculate their unborn child's gestational age. *See* P. Taipale & V. Hiilesmaa, *Predicting delivery date by ultrasound and last menstrual period in early gestation*, 97 OBSTETRICS GYN. 189 (2001); David A. Savitz et al., *Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination*, 187 AM. J. OBSTETRICS GYN. 1660 (2002).

[51] This incident also demonstrates that even where ultrasounds are used, only a qualified provider can assure they are done properly.

The resulting rupture "led to massive infection and a collapse of her vital systems." *Id.* Amicus Human Coalition identified four of their clients who were unknowingly ectopic when they arrived at their clinic "with abortion pills in hand." ECF No. 96 at 20. And at least two women died from chemical abortion drugs last year. *See* ECF No. 120 at 30 n.5. One of those women was an estimated twenty-one weeks pregnant. *See id.* Presumably, the fact that the woman obtained chemical abortion drugs more than two months past FDA's gestational age cutoff suggests that no adequate procedures confirmed the gestational age in her case.

FDA has also reported at least ninety-seven cases where women with ectopic pregnancies took mifepristone.[52] But these data are likely incomplete because FDA now only requires reporting on deaths. *See* ECF No. 1 at 4. And as noted above, hospitals often miscode complications from chemical abortions as miscarriages. Studies show that women are thirty percent more likely to die from a ruptured ectopic pregnancy while seeking abortions if the condition remains undiagnosed.[53] A woman may interpret the warning signs of an ectopic pregnancy — cramping and severe bleeding — as side effects of mifepristone. In reality, the symptoms indicate her life is in danger.[54] Another study revealed that of 5,619 chemical abortion visits, 452 patients had a pregnancy of "unknown location" and 31 were treated for ectopic pregnancy — including 4 that were ruptured.[55] Yet another study examined 3,197 unique, U.S.-only adverse event reports dated September 2000

[52] FDA, *Mifepristone US. Post-Marketing Adverse Events Summary Through 6/30/2022,* http://www.fda.gov/media/164331/download.

[53] H.K. Atrash et al., *Ectopic pregnancy concurrent with induced abortion: incidence and mortality*, 162 AM. J. OBSTETRICS GYN. 726 (1990).

[54] *Id.*

[55] Alisa B. Goldberg et al., *Mifepristone and Misoprostol for Undesired Pregnancy of Unknown Location*, 139 OBSTETRICS GYN. 771, 775 (2022).

to February 2019.[56] That study noted 20 deaths, 529 life-threatening events, and 1,957 *severe* adverse events before concluding that a pre-abortion ultrasound "should be required to rule out ectopic pregnancy and confirm gestational age."[57]

The record confirms FDA once shared these concerns. After all, many tragedies could be avoided by auditing physician qualifications and requiring ultrasounds. In 1996, the FDA Advisory Committee expressed to the Population Council "serious reservations" on how the drugs were described "in terms of assuring safe and adequate credentialing of providers." ECF No. 1-14 at 51. Population Council initially committed to conducting post-approval studies in 1996, and FDA reiterated these requirements mere months before the September 2000 approval. *See* ECF No. 1-24 at 6 ("We remind you of your commitments dated September 16, 1996, to perform the . . . Phase 4 studies."). Those protocols would have required, *inter alia*, that the Population Council: (1) assess the long-term effects of multiple uses of mifepristone; (2) ascertain the frequency with which women follow the regimen and outcomes of those that do not; (3) study the safety and efficacy of chemical abortion in girls under the age of eighteen; and (4) ascertain the regimen's effects on children born after treatment failure.[58] ECF No. 1-28 at 32.

[56] Aultman et al., *supra* note 44.

[57] *Id.*

[58] *See* 153 Cong. Rec. S5765 (daily ed. May 9, 2007) (statement of Sen. Coburn) ("I recently learned of a woman who was given RU-486 after she had a seizure. Her physicians assumed that the seizure was life-threatening to the baby she was carrying and gave her RU-486 for a therapeutic abortion. RU–486 was not effective in her case and the woman carried the baby to term. When the baby was born at a low birth weight, it also suffered from failure to thrive. That baby has had three subsequent brain surgeries due to hydrocephalus. The baby also suffers from [idiopathic lymphocytic colitis] — an inflammatory disease of the colon, which is extremely rare in children. It is clear that RU-486 not only is unsafe in women, but it is also not completely effective. And when it is not effective, the results are devastating.").

Similarly, on February 18, 2000 — months before chemical abortion approval — FDA informed the Population Council that "adequate information ha[d] *not* been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for use as recommended." ECF No. 1-24 at 6 (emphasis added). FDA then stated the "restrictions on distribution will need to be amended." *Id.* Accordingly, FDA informed the Population Council that it would proceed under Subpart H — the *only* provision that could implement the requisite restrictions on distribution. *Id.* But as explained above, that was the improper regulation for the approval of chemical abortion. Regardless, the restrictions were insufficient to ensure safe use.

On June 1, 2000, FDA privately delivered to the Population Council a set of proposed restrictions to rectify the safety issues. Said proposal required physicians who were: (1) "trained and authorized by law" to perform surgical abortions; (2) trained in administering mifepristone and treating adverse events; and (3) allowed "continuing access (*e.g.*, admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [one hour's] drive from the treatment facility." *See* ECF No. 1-14 at 53–54. When FDA's proposal was leaked to the press, a political and editorial backlash ensued.[59] In response, the Population Council rejected the proposal and repudiated the restrictions the sponsor *itself* proposed in 1996 — what FDA deemed a "very significant change" in the sponsor's position. *Id.* at 50. Because "[t]he whole idea of mifepristone was to increase access," abortion advocates argued that restrictions on mifepristone "would effectively eliminate" the drug's "main advantage" and would "kill[] the drug."[60]

[59] Sheryl Gay Stolberg, *FDA Adds Hurdles in Approval of Abortion Pill*, THE NEW YORK TIMES (June 8, 2000), https://www.nytimes.com/2000/06/08/us/fda-adds-hurdles-in-approval-of-abortion-pill.html.

[60] *Id.*

In September 2000, FDA abandoned its safety proposals and acquiesced to the objections of the Population Council and Danco. Despite its "serious reservations" about mifepristone's safety, FDA approved a regimen that relied on a self-certification that a prescribing physician has the *ability* to diagnose ectopic pregnancies. *Id.* at 51, 62; *see also* ECF No. 1-28 at 21 ("[W]e concluded that there was no need for special certification programs or additional restrictions."). FDA later released the applicant *entirely* from its Phase 4 duties — *twelve years* after the 1996 commitment. ECF Nos. 1-24 at 6, 1-28 at 32; *see also* 21 C.F.R. § 314.510 ("Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty . . . of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies *already underway*.") (emphasis added).

FDA *must* refuse to approve a drug if the agency determines there is "insufficient information to determine whether such drug is safe for use" or a "lack of substantial evidence that the drug will have the effect it purports or is represented to have" under the conditions of use in the proposed label. 21 U.S.C. § 355(d)(4)–(5); *see also* 21 C.F.R. § 314.125(b). FDA is therefore required to deny an NDA if it makes the exact findings FDA made in its 2000 review. "[A]n agency's decision to change course may be arbitrary and capricious if the agency ignores or countermands its earlier factual findings without reasoned explanation for doing so." *F.C.C. v. Fox Television Stations, Inc.*, 556 U.S. 502, 537 (2009). The agency must ordinarily "display awareness that it *is* changing position," and "must show that there are good reasons for the new policy." *Id.* at 515. And "if the agency's decision was in any material way influenced by political concerns it should not be upheld." *Earth Island Inst. v. Hogarth*, 494 F.3d 757, 768 (9th Cir. 2007). FDA's only acknowledgments of its prior proposals were that "FDA and the applicant were not always in

full agreement about the distribution restrictions" and that fulfilling the Phase 4 commitments "would not be feasible." ECF No. 1-28 at 18, 32–33.

The Court does not second-guess FDA's decision-making lightly. But here, FDA acquiesced on its legitimate safety concerns — in violation of its statutory duty — based on plainly unsound reasoning and studies that did not support its conclusions. There is also evidence indicating FDA faced significant political pressure to forego its proposed safety precautions to better advance the *political* objective of increased "access" to chemical abortion — which was the "whole idea of mifepristone."[61] As President Clinton's Secretary for Health & Human Services ("HHS") explained to the White House, it was *FDA* that arranged the meeting between the French pharmaceutical firm — who owned the mifepristone patent rights — and the eventual drug sponsor Population Council. The purpose of the FDA-organized meeting was "to facilitate an agreement between those parties to work together to test [mifepristone] and file a new drug application." ECF No. 95 at 14. HHS also "initiated" another meeting "to assess how the United States Government" — *i.e.*, the Clinton Administration — "might facilitate successful completion of the negotiations" between the French firm and the American drug sponsor to secure patent rights and eventual FDA approval. *Id.* at 16. In fact, for their "negotiations [to be] successfully concluded," the HHS Secretary believed American pressure on the French firm was necessary. [62] *Id.*

Whether FDA abandoned its proposed restrictions because of political pressure or not, one thing is clear: the lack of restrictions resulted in many deaths and many more severe or life-

[61] Stolberg, *supra* note 59.

[62] *See also* Lars Noah, *A Miscarriage in the Drug Approval Process?: Mifepristone Embroils the FDA in Abortion Politics*, 36 WAKE FOREST L. REV. 571, 576 (2001) ("The Clinton administration went to great lengths to bring mifepristone into the United States. From pressuring the hesitant manufacturer to apply for approval, and utilizing a specialized review procedure normally reserved for life-saving drugs, to imposing unusual restrictions on distribution, and promising to keep the identity of the manufacturer a secret, the FDA's approval process deviated from the norm in several respects.").

threatening adverse reactions. Due to FDA's lax reporting requirements, the exact number is not ascertainable. But it is likely far higher than its data indicate for reasons previously mentioned. Whatever the numbers are, they likely would be considerably lower had FDA not acquiesced to the pressure to increase access to chemical abortion at the expense of women's safety. FDA's failure to *insist* on the inclusion of its proposed safety restrictions was not "the product of reasoned decisionmaking." *State Farm*, 463 U.S. at 52. To hold otherwise would be "tantamount to abdicating the judiciary's responsibility under the [APA] to set aside agency actions that are 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.'" *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1491 (D.C. Cir. 1995) (quoting 5 U.S.C. § 706(2)(A)). Finally, the 2000 Approval was also arbitrary and capricious because it violated Subpart H.[63]

b. The 2016 Changes

FDA made numerous substantial changes to the chemical abortion regimen in 2016. These changes include but are not limited to: (1) eliminating the requirement for prescribers to report *all* nonfatal serious adverse events; (2) extending the maximum gestational age from 49 days to 70 days; (3) eliminating the requirement that administration of misoprostol occurs in-clinic; (4) removing the requirement for an in-person follow-up exam; and (5) allowing "healthcare providers" other than physicians to dispense chemical abortion drugs. ECF No. 1 at 53–54. Plaintiffs allege the 2016 Changes were also arbitrary and capricious "because *none* of the studies on which FDA relied were designed to evaluate the safety and effectiveness of chemical abortion

[63] As one scholar noted, "the agency took this route so that it could better justify imposing otherwise unauthorized restrictions on the use and distribution of the drug." *See* Noah, *supra* note 62, at 582. And "while agency action may generally be 'entitled to a presumption of regularity,' here FDA itself acknowledges that its action has not been regular: it failed to respond to the Citizen Petition for years." *Bayer*, 942 F. Supp. 2d at 25 (internal marks omitted). At the hearing, Defendants' leading argument for Subpart H was that "none of it really matters" because of the FDAAA. *See* ECF No. 136 at 100. "This is not the argument of an agency that is confident in the legality of its actions." ECF No. 100 at 15.

drugs for use under the conditions prescribed, recommended, or suggested in the proposed labeling." ECF No. 7 at 24.

For similar reasons as the 2000 Approval, the Court agrees. Unlike the crucial studies FDA relied upon to extend the maximum gestational age, change the dosing regimen, and authorize a repeat dose of misoprostol, the labeling approved by FDA in 2016 did *not* require: (1) an ultrasound; (2) an in-person follow-up exam; or (3) the ability of abortionists to personally perform a surgical abortion if necessary. *Id.* Simply put, FDA built on its already-suspect 2000 Approval by removing *even more* restrictions related to chemical abortion drugs that were present during the final phase of the investigation. And it did so by relying on studies that included the very conditions FDA refused to adopt.[64] None of the studies compared the safety of the changes against the then-current regimen, nor under the labeled conditions of use. Moreover, FDA shirked any responsibility for the consequences of its actions by eliminating any requirement that non-fatal adverse events be reported. Thus, FDA took its chemical abortion regimen — which had already culminated in *thousands* of adverse events suffered by women and girls — and removed what little restrictions protected these women and girls, systematically ensuring that almost all new adverse events would go unreported or underreported.

Defendants aver that "Plaintiffs point to no statutory provision requiring the conditions of use in a drug's approved labeling to duplicate the protocol requirements used in the studies supporting its approval." ECF No. 28 at 32. "The [FFDCA] thus requires FDA to apply its scientific expertise in determining whether a drug has been shown to be safe and effective under particular conditions of use, and the application of that expertise is owed substantial deference." *Id.* But FDA does not have unfettered discretion to approve dangerous drugs under substantially

[64] *See* ECF No. 1-35.

different conditions than the tests, trials, and studies cited. To be clear, the Court does not hold that *any* difference between approval conditions and testing conditions — no matter how well-justified — means the approval fails as a matter of law. But the agency "must cogently explain why it has exercised its discretion in a given manner," and that explanation must be "sufficient to enable [the Court] to conclude that the [agency's action] was the product of reasoned decisionmaking." *A.L. Pharma*, 62 F.3d at 1491 (quoting *State Farm*, 463 U.S. at 52). Defendants have not done so here. FDA's 2016 Actions were not the product of reasoned decision-making.

c. The 2019 Generic Approval

The FFDCA allows a generic drug manufacturer to submit an ANDA for premarket review and approval. 21 U.S.C. § 355(j); 21 C.F.R. § 314.94. The generic sponsor must show that: (1) the conditions of use prescribed, recommended, or suggested in the labeling have been previously approved; and (2) the drug product is chemically the same as the already approved drug — allowing it to rely on FDA's previous finding of safety and effectiveness for the approved drug. *Id.* On April 11, 2019, FDA approved GenBioPro, Inc.'s ANDA for a generic version of mifepristone. ECF No. 7 at 10. In doing so, FDA relied on Mifeprex's safety data. *Id.*

Plaintiffs argue the 2019 Approval was unlawful because FDA relied on the unlawful 2000 Approval and its unlawful 2016 Changes when approving generic mifepristone. ECF No. 7 at 27. If FDA withdraws the listed drug on which the ANDA-approved generic drug is based, the agency is generally required to withdraw the generic drug as well. 21 U.S.C. § 355(j)(6); 21 C.F.R. § 314.151. Because the Court agrees that Plaintiffs have a substantial likelihood of success in their challenges to the 2000 and 2016 Actions, the Court is inclined to agree with Plaintiffs on this claim as well.

E. There Is a Substantial Threat of Irreparable Harm

To satisfy the second element of the preliminary injunction standard, Plaintiffs "must demonstrate that if the district court denied the grant of a preliminary injunction, irreparable harm would result." *Janvey*, 647 F.3d at 600 (internal marks omitted). "In general, a harm is irreparable where there is no adequate remedy at law, such as monetary damages." *Id.* (internal marks omitted). "When determining whether injury is irreparable, it is not so much the magnitude but the irreparability that counts." *Texas v. U.S. Env't Prot. Agency*, 829 F.3d 405, 433–34 (5th Cir. 2016) (internal marks omitted). Where "the likelihood of success on the merits is very high, a much smaller quantum of injury will sustain an application for preliminary injunction." *Mova Pharm. Corp. v. Shalala*, 955 F. Supp. 128, 131 (D.D.C. 1997), *aff'd,* 140 F.3d 1060 (D.C. Cir. 1998) (citing *Cuomo v. U.S. Nuclear Regul. Comm'n*, 772 F.2d 972, 974 (D.C.Cir. 1985) (per curiam)). Plaintiffs' Motion satisfies this standard.

For reasons already stated, Plaintiffs are likely to suffer irreparable harm if the Motion is not granted. At least two women died from chemical abortion drugs just last year. *See* ECF No. 120 at 30 n.5;[65] *Deerfield Med. Ctr. v. City of Deerfield Beach*, 661 F.2d 328, 338 (5th Cir. 1981) (finding irreparable harm to third-party pregnant women). "The physical and emotional trauma that chemical abortion inflicts on women and girls cannot be reversed or erased." ECF No. 7 at 28; *see also E.E.O.C. v. Chrysler Corp.*, 733 F.2d 1183, 1186 (6th Cir. 1984) (affirming irreparable harm for plaintiffs' "emotional distress"). "The crucial time that doctors need to treat these injured women and girls cannot be replaced." *Id.* "The mental and monetary costs to these doctors cannot be repaid." *Id.* "And the time, energy and resources that Plaintiff medical associations expend in

[65] One of those women was reportedly twenty-one weeks pregnant, which is well past the cutoff for gestational age even after the 2016 Changes. *See id.* The other maternal death occurred while the woman was seven weeks pregnant, which falls within FDA's current restrictions. *Id.*

response to FDA's actions on chemical abortion drugs cannot be recovered." *Id.*; *see also Whitman-Walker Clinic, Inc. v. U.S. Dep't of Health & Hum. Servs.*, 485 F. Supp. 3d 1, 56 (D.D.C. 2020) (obstacles that make it more difficult for an organization to accomplish its mission provide injury for both standing *and* irreparable harm).

Defendants' respond that the drugs at issue have been on the market for more than twenty years. ECF No. 28 at 41. This argument ignores that many restrictions and safeguards — which no longer exist — were in place for most of that time. Defendants also argue "Plaintiffs' extreme delay" in filing suit shows they face no irreparable harm. *Id.* at 42. But the time between the allegedly unlawful actions and the filing of a suit "is not determinative" of whether relief should be granted. *Boire v. Pilot Freight Carriers, Inc.*, 515 F.2d 1185, 1193 (5th Cir. 1975). Here, eleven months does not constitute an "extreme" delay. *See, e.g.*, *Optimus Steel, LLC v. U.S. Army Corps of Eng'rs*, 492 F. Supp. 3d 701, 720 (E.D. Tex. 2020) (eleven-month delay did not militate against equitable relief because "the Court can presume that Plaintiff needed ample time to evaluate its claims").[66] "[T]emporary injunctive relief may still be of great value to protect against ongoing harms, even if the initial harm is in the distant past." *N.L.R.B. v. Hartman & Tyner, Inc.*, 714 F.3d 1244, 1252 (11th Cir. 2013).

The Court also disagrees that Plaintiffs' theories of injury "are too speculative to even show standing." ECF No. 28 at 42. Plaintiffs have credibly alleged past and future harm resulting from the removal of restrictions for chemical abortion drugs. "Although a court's analysis of likelihood of success in the context of an injunctive relief request is governed by the deferential APA's arbitrary and capricious standard, a court does not always owe deference to federal agencies' positions concerning irreparable harm, balance of hardships, or public interest." *San Luis & Delta-*

[66] To clarify, the eleven months referenced here is the approximate time between FDA's "final agency action" in the December 2021 Denial of the 2019 Petition and the commencement of this case.

Mendota Water Auth. v. Jewell, 969 F. Supp. 2d 1211, 1215 (E.D. Cal. 2013); *see also R.J. Reynolds Vapor Co. v. FDA*, No. 23-60037 (5th Cir. Mar. 23, 2023)[67] (noting FDA's public interest argument was "obviously colored by the FDA's view of the merits"); *Sierra Forest Legacy v. Sherman*, 646 F.3d 1161, 1186 (9th Cir. 2011) ("If the federal government's experts were always entitled to deference concerning the equities of an injunction, substantive relief against federal government policies would be nearly unattainable, as government experts will likely attest that the public interest favors the federal government's preferred policy.").

F. Preliminary Injunction Would Serve the Public Interest

The third and fourth factors — assessing the harm to the opposing party and weighing the public interest — "merge when the Government is the opposing party." *Nken v. Holder*, 556 U.S. 418, 435 (2009). "[T]he public interest weighs strongly in favor of preventing unsafe drugs from entering the market." *Hill Dermaceuticals*, 524 F. Supp. 2d at 12. "[T]here is generally no public interest in the perpetuation of unlawful agency action." *State v. Biden*, 10 F.4th 538, 560 (5th Cir. 2021) (internal marks omitted). And "there is a strong public interest in meticulous compliance with the law by public officials." *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993); *see also State v. Biden*, 10 F.4th at 559. "Indeed, the Constitution itself declares a prime public interest that the President and, by necessary inference, his appointees in the Executive Branch 'take Care that the Laws be faithfully executed.'" *Id.* (internal marks omitted). Additionally, Defendants' actions harm States' efforts to regulate chemical abortion "in the interests of life, health, and liberty." ECF No. 100 at 21. "The Court appreciates FDA's institutional interest but, given its long-standing disregard of [Plaintiffs'] Citizen Petition[s], its argument has a hollow center." *Bayer HealthCare*, 942 F. Supp. 2d at 26. To the extent Defendants

[67] https://www.ca5.uscourts.gov/opinions/pub/23/23-60037-CV0.pdf.

and third parties would be harmed by an injunction, the Court still balances these factors in favor of ensuring that women and girls are protected from unnecessary harm and that Defendants do not disregard federal law.

For these reasons, a preliminary injunction would serve the public interest. Defendants maintain that *unaborted* children of the women "who seek but are unable to obtain an abortion" are "expected to do worse in school," "to have more behavioral and social issues, and ultimately to attain lower levels of completed education." ECF No. 28-2 at 7. "They are also expected to have lower earnings as adults, poorer health, and an increased likelihood of criminal involvement." *Id.* But "[u]sing abortion to promote eugenic goals is morally and prudentially debatable." *Planned Parenthood of Ind. & Ky., Inc. v. Comm'r of Ind. State Dep't of Health*, 917 F.3d 532, 536 (7th Cir. 2018) (Easterbrook, J., dissenting); *see also Box v. Planned Parenthood of Ind. & Ky., Inc.*, 139 S. Ct. 1780, 1790 (2019) (Thomas, J., concurring) ("[A]bortion has proved to be a disturbingly effective tool for implementing the discriminatory preferences that undergird eugenics."). Though eugenics were once fashionable in the Commanding Heights and High Court, they hold less purchase after the conflict, carnage, and casualties of the *last* century revealed the bloody consequences of Social Darwinism practiced by would-be Übermenschen. *Cf. Buck v. Bell*, 274 U.S. 200, 207 (1927) ("It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes.").

Defendants are correct that one purpose of injunctive relief is to preserve the status quo. *See, e.g.*, *City of Dallas v. Delta Air Lines, Inc.*, 847 F.3d 279, 285 (5th Cir. 2017). But the "status quo" to be restored is "the last peaceable uncontested status existing between the parties before the

dispute developed." *Texas v. Biden*, No. 2:21-CV-067-Z, 2022 WL 17718634, at *9 (N.D. Tex. Dec. 15, 2022) (internal marks omitted); *see also Texas v. United States*, 40 F.4th 205, 220 (5th Cir. 2022) (the relevant status quo is the one "absent the unlawful agency action"); *Wages & White Lion*, 16 F.4th at 1144 ("In other words, 'the relief sought here would simply suspend *administrative* alteration of the *status quo*.'") (quoting *Nken*, 556 U.S. at 430 n.1); *Callaway*, 489 F.2d at 576 ("If the currently existing status quo itself is causing one of the parties irreparable injury, it is necessary to alter the situation so as to prevent the injury."). "[P]arties could otherwise have no real opportunity to seek judicial review except at their peril." Mila Sohoni, *The Power to Vacate a Rule*, 88 GEO. WASH. L. REV. 1121, 1157–58 (2020). Chemical abortion is only the status quo insofar as Defendants' unlawful actions and their delay in responding to Plaintiffs' petitions have made it so. The fact that injunctive relief could upset this "status quo" is therefore an insufficient basis to deny injunctive relief.

G. A Stay Under Section 705 of the APA Is More Appropriate Than Ordering Withdrawal or Suspension of FDA's Approval

The Motion asks for injunctive relief but goes as far as requesting the Court to order Defendants to "withdraw or suspend the approvals of chemical abortion drugs, and remove them from the list of approved drugs." ECF No. 7 at 7. Singular equitable relief is "commonplace" in APA cases and is often "necessary to provide the plaintiffs" with "complete redress." *E. Bay Sanctuary Covenant v. Biden*, 993 F.3d 640, 681 (9th Cir. 2021) (internal marks omitted). Although the Court finds Plaintiffs have a substantial likelihood of prevailing on the merits, the Court instead exercises its authority under the APA to order less drastic relief. Section 705 of the APA provides:

> When an agency finds that justice so requires, it may postpone the effective date of action taken by it, pending judicial review. On such conditions as may be required and to the extent necessary to prevent irreparable injury, the reviewing court, including the court to which a case may be taken on appeal from or on application for certiorari or other writ to a reviewing court, *may issue all necessary and appropriate process to postpone the effective date of an agency action* or to preserve status or rights pending conclusion of the review proceedings.

5 U.S.C. § 705 (emphasis added).

The Fifth Circuit has acknowledged "meaningful differences between an injunction, which is a 'drastic and extraordinary remedy,' and vacatur, which is 'a less drastic remedy.'" *Texas v. Biden*, 2022 WL 17718634 at *7 (quoting *Texas v. United States*, 40 F.4th at 219). Whereas an injunction "tells someone what to do or not to do," a vacatur only reinstates "the status quo absent the unlawful agency action and neither compels nor restrains further agency decision-making." *Id.* (internal marks omitted). A Section 705 stay can "be seen as an interim or lesser form of vacatur under Section 706." *Id.* "Just as a preliminary injunction is often a precursor to a permanent injunction, a stay under Section 705 can be viewed as a precursor to vacatur under Section 706." *Id.*; *see also Nken*, 556 U.S. at 428–29 (a stay "temporarily suspend[s] the source of authority to act — the order or judgment in question — not by directing an actor's conduct"). "Motions to stay agency action pursuant to [Section 705] are reviewed under the same standards used to evaluate requests for interim injunctive relief." *Id.* at *10 (citing *Affinity Healthcare Servs., Inc. v. Sebelius*, 720 F. Supp. 2d 12, 15 n.4 (D.D.C. 2010)); *see also Nken*, 556 U.S. at 434; *Texas v. U.S. Env't Prot. Agency*, 829 F.3d at 435. Because the Court finds injunctive relief is generally appropriate, Section 705 plainly authorizes the lesser remedy of issuing "all necessary and appropriate process" to postpone the effective date of the challenged actions. "Courts — including the Supreme Court — routinely stay *already-effective* agency action under Section 705." *Id.* at *8 (emphasis added) (collecting cases).

Accordingly, the Court hereby **STAYS** the effective date of FDA's September 28, 2000, Approval of mifepristone and all subsequent challenged actions related to that approval — *i.e.*, the 2016 Changes, the 2019 Generic Approval, and the 2021 Actions. This Court acknowledges that its decision in *Texas v. Biden* has been appealed to the Fifth Circuit. *See* 2:21-CV-067-Z, ECF No. 184 (Feb. 13, 2023). If the Fifth Circuit reverses this Court's Section 705 analysis, the Court clarifies that it alternatively would have ordered Defendants to suspend the chemical abortion approval and all subsequent challenged actions related to that approval until the Court can render a decision on the merits.

CONCLUSION

For the foregoing reasons, the Court **GRANTS** the Motion **IN PART**. FDA's approval of mifepristone is hereby **STAYED**. The Court **STAYS** the applicability of this opinion and order for seven (7) days to allow the federal government time to seek emergency relief from the United States Court of Appeals for the Fifth Circuit.

SO ORDERED.

April 7, 2023

MATTHEW J. KACSMARYK
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its member organizations, their members, and these members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration; **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

COMPLAINT

1. The U.S. Food and Drug Administration (FDA) must protect the health, safety, and welfare of all Americans by rejecting or limiting the use of dangerous drugs.

2. But the FDA failed America's women and girls when it chose politics over science and approved chemical abortion drugs for use in the United States. And it has continued to fail them by repeatedly removing even the most basic precautionary requirements associated with their use.

3. To date, the FDA's review, approval, and deregulation of chemical abortion drugs has spanned three decades, correlated with four U.S. presidential elections, and encompassed six discrete agency actions. Plaintiffs challenge these six FDA actions and ask that the Court hold them unlawful, set them aside, and vacate them.

4. Beginning in January 1993, on his second full day in office, President Bill Clinton directed his cabinet to legalize chemical abortion drugs in the United States.

5. President Clinton and his agency officials then pressured the French manufacturer of the key chemical abortion drug, mifepristone (also known as "RU-486" and "Mifeprex"), to *donate for free* the U.S. patent rights of the drug to the Population Council—as its name suggests, an entity focused on population control.

6. After receiving the patent rights to mifepristone, the Population Council submitted a new drug application, worked closely with the Clinton FDA during the review process, and, not surprisingly, obtained the agency's approval on

September 28, 2000—just over one month before the closely contested 2000 U.S. presidential election.

7. The *only* way the FDA could have approved chemical abortion drugs was to use its accelerated drug approval authority, necessitating the FDA to call pregnancy an "illness" and argue that these dangerous drugs provide a "meaningful therapeutic benefit" over existing treatments.

8. But pregnancy is not an illness, nor do chemical abortion drugs provide a therapeutic benefit over surgical abortion. In asserting these transparently false conclusions, the FDA exceeded its regulatory authority to approve the drugs.

9. What's more, the FDA needed to disavow science and the law because the FDA never studied the safety of the drugs under the labeled conditions of use despite being required to do so by the Federal Food, Drug, and Cosmetic Act (FFDCA). The agency also ignored the potential impacts of the hormone-blocking regimen on the developing bodies of adolescent girls in violation of the Pediatric Research and Equity Act (PREA). And the FDA disregarded the substantial evidence that chemical abortion drugs cause more complications than even surgical abortions.

10. Since then, the FDA has not followed the science, reversed course, or fixed its mistakes—all to the detriment of women and girls. Instead, the FDA has doubled down on its actions and removed the few safeguards that were in place.

11. In March 2016—*fourteen years* after two Plaintiffs filed a citizen petition with the FDA asking the agency to withdraw its approval of chemical

abortion drugs—the FDA rejected these Plaintiffs' petition despite their explanations that the agency violated federal laws by approving these drugs and ignoring the substantial evidence that these drugs harm women and girls.

12. On the *same day* that the FDA rejected the citizen petition and mere months before another U.S. presidential election, the FDA also made "major changes" to the chemical abortion drug regimen, eliminating crucial safeguards for pregnant women and girls.

13. For example, the FDA extended the permissible gestational age of the baby for which a pregnant woman or girl may take chemical abortion drugs—from seven weeks to ten weeks.

14. Numerous studies have demonstrated that there is an increased risk from chemical abortion drugs to pregnant women and girls as the baby's age advances from seven weeks to ten weeks because the surface area of the placenta as well as the size of the baby significantly grow during these three weeks.

15. Also in 2016, the FDA changed the dosage and route of administration for the chemical abortion drugs, reduced the number of required in-person office visits from three to one, expanded who could prescribe and administer chemical abortion drugs beyond medical doctors, and eliminated the requirement for abortionists to report non-fatal complications from chemical abortion drugs—without requiring any objective clinical investigations or studies that evaluated the safety and effectiveness of this new chemical abortion regimen or any safety assessment of its effects on the developing bodies of girls under 18 years of age.

16. These major changes failed to satisfy the rigorous scientific standards of the FFDCA and violated PREA's requirement for a specific safety assessment of these changes on pregnant girls who undergo the revised chemical abortion drug regimen.

17. Realizing a profit-making opportunity in the rapidly growing chemical abortion business, another entity sought the FDA's approval to market and distribute a generic version of mifepristone. In 2019, the FDA obliged and approved the generic drug—without requiring any new clinical investigations or studies that evaluated the drug's safety and effectiveness under the requirements of the FFDCA, nor any specific safety assessments on girls as set forth under PREA.

18. A couple of years later, in April of 2021, shortly after President Joe Biden took office, the FDA's new management issued a "Non-Enforcement Decision" by which the agency would stop enforcing its requirement that abortionists provide in-person dispensing of mifepristone and instead would temporarily allow mail-order chemical abortions during the COVID-19 public health emergency.

19. In December 2021—*two-and-a-half years* after two Plaintiffs filed a citizen petition asking the FDA to restore and strengthen the pre-2016 chemical abortion drug regimen or, at minimum, to preserve the few remaining safeguards for women and girls—the FDA rejected almost all of these Plaintiffs' citizen petition. The FDA issued its denial despite their discussion of how the agency violated the law by ignoring the growing and substantial evidence that these dangerous drugs harm women and girls.

20. On the *same day* that it rejected the citizen petition, the Biden FDA also announced that it would permanently allow abortionists to send chemical abortion drugs through the mail.

21. This decision not only harms women and girls who voluntarily undergo chemical abortions, but it also further helps sex traffickers and sexual abusers to force their victims into getting abortions while preventing the authorities from identifying these victims.[1] In fact, the State of Texas has recognized that "[d]ue to the potentially high number of trafficking victims who undergo abortion procedures, abortion facility employees are uniquely situated to identify and assist victims of sex trafficking."[2]

22. In addition to the legal and scientific infirmities referenced above, all of the FDA's actions on chemical abortion drugs—the 2000 approval, the 2016 major changes, the 2019 generic drug approval, and the two 2021 actions to eliminate the in-person dispensing requirement—failed to acknowledge and address the federal laws that prohibit the distribution of chemical abortion drugs by postal mail,

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[1] *See, e.g.,* Ex. 1, Laura J. Lederer & Christopher A. Wetzel, *The Health Consequences of Sex Trafficking and Their Implications for Identifying Victims in Healthcare Facilities*, Annals of Health Law, Winter 2014 at 61Laura J. Lederer & Christopher A. Wetzel, *The Health Consequences of Sex Trafficking and Their Implications for Identifying Victims in Healthcare Facilities*, Annals of Health Law, Winter 2014 at 61, 73, 77–78 (noting that survivors in study "reported that they often did not freely choose the abortions they had while being trafficked," these "[s]urvivors [] had significant contact with clinical treatment facilities, most commonly Planned Parenthood clinics," and that "these points of contact with healthcare represent rare opportunities for victim identification and intervention.").

[2] Ex. 2, C.S.H.B. 3446, H. Comm. Rpt., 84th Legis. (Mar. 12, 2015), https://capitol.texas.gov/tlodocs/84R/analysis/pdf/HB03446H.pdf (a subsequent, similar version was codified at Tex. Health & Safety Code § 245.025).

express company, or common carrier. *See* 18 U.S.C. §§ 1461, 1462. Instead, the FDA's actions permitted and sometimes even encouraged these illegal activities.

23. After two decades of engaging the FDA to no avail, Plaintiffs now ask this Court to do what the FDA was and is legally required to do: protect women and girls by holding unlawful, setting aside, and vacating the FDA's actions to approve chemical abortion drugs and eviscerate crucial safeguards for those who undergo this dangerous drug regimen.

JURISDICTION AND VENUE

24. This Court has subject-matter jurisdiction under 28 U.S.C. § 1331 because this action raises federal questions under the Administrative Procedure Act (APA), 5 U.S.C. §§ 553, 701–06, and the FFDCA, 21 U.S.C. § 301 *et seq*.

25. This Court also has jurisdiction under 28 U.S.C. § 1346(a) because this is a civil action against the United States.

26. Additionally, this Court has jurisdiction under 28 U.S.C. § 1361 to compel an officer of the United States or any federal agency to perform his or her duty.

27. This Court has jurisdiction to review Defendants' unlawful actions and enter appropriate relief under the APA, 5 U.S.C. §§ 553, 701–06.

28. This Court has jurisdiction to issue equitable relief to enjoin ultra vires agency action under an equitable cause of action. *Larson v. Domestic & Foreign Com. Corp.*, 337 U.S. 682, 689–91 (1949).

29. This case seeks declaratory, injunctive, and other appropriate relief under the Declaratory Judgment Act, 28 U.S.C. §§ 2201–02, 5 U.S.C. §§ 705–06, Federal Rule of Civil Procedure 57, and the Court's inherent equitable powers.

30. This Court may award costs and attorneys' fees under the Equal Access to Justice Act, 28 U.S.C. § 2412.

31. Venue is proper in this Court under 28 U.S.C. § 1391 because a substantial part of the events or omissions giving rise to the claims occurred in this district, and a substantial part of property that is the subject of the action is situated here. This district and this division are where Plaintiffs Alliance for Hippocratic Medicine, including the doctors of its member associations, and Dr. Shaun Jester are situated and are injured by Defendants' actions. Defendants are United States agencies or officers sued in their official capacities. A substantial part of the events or omissions giving rise to the Complaint occurred within the Northern District of Texas.

PLAINTIFFS

32. Four national medical associations and four doctors experienced in caring for pregnant and post-abortive patients bring this case. They seek to protect women and girls from the documented dangers of chemical abortion drugs.

33. Plaintiff Alliance for Hippocratic Medicine is a nonprofit membership organization that upholds and promotes the fundamental principles of Hippocratic medicine: protecting the vulnerable at the beginning and end of life; seeking the ultimate good for the patient with compassion and moral integrity; and providing health care with the highest standards of excellence based on medical science. The

Alliance for Hippocratic Medicine's members currently are the American Association of Pro-Life Obstetricians and Gynecologists, the American College of Pediatricians, the Catholic Medical Association, the Christian Medical & Dental Associations, and the Coptic Medical Association of North America. The Alliance for Hippocratic Medicine is incorporated in the State of Texas and has its registered agent in Amarillo, Texas. The Alliance for Hippocratic Medicine seeks relief on behalf of itself, its current and future member organizations, their members, and these members' patients. Mr. Mario Dickerson and Drs. Donna Harrison, Jeffrey Barrows, and Quentin Van Meter submit declarations in support of the Alliance for Hippocratic Medicine.[3]

34. Plaintiff American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG) is a nonprofit organization that encourages and equips its members and other concerned medical practitioners to provide an evidence-based rationale for defending the lives of both the pregnant mother and her unborn child. AAPLOG aims to make known the evidence-based effects of abortion on women as well as the scientific fact that human life begins at the moment of fertilization, with the goal that all women, regardless of race, creed, or national origin, will be empowered to make healthy and life-affirming choices. AAPLOG is incorporated in the State of Florida, and headquartered in Indiana. AAPLOG has individual members in Texas. AAPLOG seeks relief on behalf of itself, its current and future

[3] Ex. 3, Dickerson Decl. ¶ 7; Ex. 4, Harrison Decl. ¶ 6, 13; Ex. 5, Barrows Decl. ¶ 2; Ex. 6, Van Meter Decl. ¶ 6.

members, and their patients. Drs. Donna Harrison, Christina Francis, Ingrid Skop, and Nancy Wozniak submit declarations in support of AAPLOG.[4]

35. Plaintiff American College of Pediatricians is a national organization of pediatricians and other health care professionals. The American College of Pediatricians is a nonprofit organization founded in 2002, is incorporated in the State of Tennessee, and has its registered agent in Tennessee. The American College of Pediatricians' membership includes more than 600 physicians and other health care professionals drawn from 47 different states across the nation. The American College of Pediatricians has members within this judicial district and elsewhere in the State of Texas. The American College of Pediatricians seeks relief on behalf of itself, its current and future members, and their patients. Dr. Quentin Van Meter submits a declaration in support of the American College of Pediatricians.[5]

36. Plaintiff Christian Medical & Dental Associations is a national nonprofit organization, headquartered in the State of Tennessee, of Christian physicians, dentists, and allied health care professionals, with over 13,000 members nationwide, including 1,237 overall members in Texas, of whom 607 are practicing or retired physicians, and 35 are OB/Gyns. The Christian Medical & Dental Associations sues on behalf of itself, its current and future members, and their

[4] Ex. 4, Harrison Decl. ¶ 5; Ex. 7, Francis Decl. ¶ 4; Ex. 8, Skop Decl. ¶ 4; Ex. 9, Wozniak Decl. ¶ 3.

[5] Ex. 6, Van Meter Decl. ¶ 6.

patients. Drs. Jeffrey Barrows and Steven Foley submit declarations in support of the Christian Medical & Dental Associations.[6]

37. Plaintiff Dr. Shaun Jester, D.O, is a board-certified obstetrician and gynecologist and the Medical Director of Moore County OB/Gyn in Dumas, Texas. His practice includes cesarean section deliveries, hysterectomies, and other women's health treatments. He has treated women who have had abortions, including one woman who suffered an adverse event from a chemical abortion, for which he submitted an adverse event report to the FDA. Dr. Jester sues on his own behalf and on behalf of his current and future patients.

38. Plaintiff Dr. Regina Frost-Clark, M.D., is a board-certified doctor in obstetrics and gynecology. She practices with Ascension Medical Group St. John OB/Gyn Associates in Saint Clair Shores, Michigan. Dr. Frost-Clark has treated several women who have suffered complications from chemical abortions, many who presented to the emergency room. Dr. Frost-Clark sues on her own behalf and on behalf of her current and future patients.

39. Plaintiff Dr. Tyler Johnson, D.O., is an emergency department physician certified by the American Board of Emergency Medicine. Based out of Leo, Indiana, Dr. Johnson serves as the director of emergency medicine at Parkview Dekalb Hospital and practices in the emergency departments of hospitals throughout northern Indiana. He has treated women in the emergency department

[6] Ex. 5, Barrows Decl. ¶ 2; Ex. 10, Foley Decl. ¶ 5.

suffering complications from chemical abortion. Dr. Johnson sues on his own behalf and on behalf of his current and future patients.

40. Plaintiff Dr. George Delgado, M.D., is board-certified in family medicine and in hospice and palliative medicine. He serves as the director of medical affairs of Culture of Life Family Services, which based out of Escondido, California, and provides comprehensive medical care and pro-life pregnancy clinic services for women and children. He also serves as a medical advisor to the Abortion Pill Rescue Network. Dr. Delgado established the Abortion Pill Reversal program—a process that can reverse the effects of the chemical abortion drug regimen and allow women and girls to continue their pregnancies.[7] He has treated women suffering complications from chemical abortion and seeking to reverse the effects of chemical abortion. Dr. Delgado sues on his own behalf and on behalf of his current and future patients.

DEFENDANTS

41. Defendant FDA is an agency of the United States government within the United States Department of Health and Human Services (HHS). The Secretary of HHS has delegated to the FDA the authority to administer the provisions of the FFDCA for approving new drug applications and authorizing a risk evaluation and mitigation strategy (REMS) for dangerous drugs. The address of the FDA's headquarters is 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

[7] Abortion Pill Reversal, https://www.abortionpillreversal.com/abortion-pill-reversal/overview (last visited Nov. 17, 2022).

42. Defendant Robert Califf, M.D., who is being sued in his official capacity, is the Commissioner of Food and Drugs at the FDA. He is responsible for supervising the activities of the FDA, including the approval of new drug applications and the issuance, suspension, waiver, or removal of a REMS. Defendant Califf's address is 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

43. Defendant Janet Woodcock, M.D., who is being sued in her official capacity, is the Principal Deputy Commissioner, Office of the Commissioner, at the FDA. She works closely with the Commissioner of Food and Drugs to develop and implement key public health initiatives and oversees the agency's day-to-day functions. Defendant Woodcock served as the Acting Commissioner of Food and Drugs from January 20, 2021, until February 17, 2022, and previously was the Director of the FDA's Center for Drug Evaluation and Research. Defendant Woodcock's address is 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

44. Defendant Patrizia Cavazzoni, M.D., who is being sued in her official capacity, is the Director of the FDA's Center for Drug Evaluation and Research. She is responsible for the regulation of drugs throughout their lifecycle, the development of new and generic drugs, the evaluation of applications to determine whether drugs should be approved, the monitoring of the safety of drugs after they are marketed, and the taking of enforcement actions to protect the public from harmful drugs.

Defendant Cavazzoni's address is 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

45. Defendant HHS is a federal agency within the executive branch of the U.S. government, including under 5 U.S.C. § 551 and 701(b)(1). Its address is 200 Independence Avenue SW, Washington, D.C. 20201.

46. Defendant Xavier Becerra is the Secretary of HHS and is sued in his official capacity. He is responsible for the overall operations of HHS, including the FDA. His address at HHS is 200 Independence Avenue SW, Washington, D.C. 20201.

47. Collectively and as applicable, all defendants are referred to herein as the "FDA" or "Defendants." Plaintiffs also sue Defendants' employees, agents, and successors in office.

48. The federal officials are subject to the APA. 5 U.S.C. § 701(b); 5 U.S.C. § 551(1).

FACTUAL ALLEGATIONS

I. Introduction

49. This case challenges the FDA's failure to abide by its legal obligations to protect the health, safety, and welfare of women and girls[8] when the agency authorized the chemical abortion drugs mifepristone and misoprostol for use in the

[8] The FDA's approval of chemical abortion lacks an age restriction and, therefore, permits the use of the drug regimen by a pregnant girl of any age under 18 years.

United States and subsequently eliminated necessary safeguards for pregnant women and girls who undergo this dangerous drug regimen.

50. *First*, the FDA never had the authority to approve these drugs for sale. In 2000, the FDA approved chemical abortion drugs under 21 C.F.R. § 314, Subpart H (Subpart H). This regulation authorizes the FDA to grant "accelerated approval" of "certain new drug products that have been studied for their safety and effectiveness in treating *serious or life-threatening illnesses* and that provide *meaningful therapeutic benefit* to patients over existing treatments." 21 C.F.R. § 314.500 (emphasis added).

51. But chemical abortion drugs do not treat serious or life-threatening illnesses. Indeed, pregnancy is a normal physiological state that many females experience one or more times during their childbearing years. Pregnancy rarely leads to complications that threaten the life of the mother or the child. Following delivery, almost all women return to a normal routine without disability.[9]

52. Likewise, chemical abortion drugs do not provide a "meaningful therapeutic benefit" to women and girls over existing treatments.

53. To the contrary, the FDA's approval of chemical abortion drugs has potentially serious and life-threatening effects on women and girls, especially when

[9] Ex. 11, Byron Calhoun, *The maternal mortality myth in the context of legalized abortion,* 80 The Linacre Quarterly 264, 264–276 (2013); James Studnicki & Tessa Longbons, *Pregnancy Is* Not *More Dangerous Than Abortion*, Nat'l Rev. (Aug. 28, 2022, 6:30 AM), https://www.nationalreview.com/2022/08/pregnancy-is-not-more-dangerous-than-abortion/.

compared to surgical abortion, which uses medical devices and tools to physically remove a baby from inside the pregnant mother.

54. Even though endocrine disruptors such as mifepristone could have significant impacts on an adolescent girl's developing body and reproductive system, the FDA never required an assessment that evaluated the safety and effectiveness of chemical abortion drugs on pregnant girls under 18 years of age.

55. *Second*, the FDA has not only continued to keep chemical abortion drugs on the market, but the agency has also eliminated the few safeguards it initially established to protect women and girls who go through the chemical abortion drug regimen.

56. In particular, in 2016, the FDA (1) increased the gestational age for which a pregnant woman or girl may have a chemical abortion from 49 days' gestation to 70 days' gestation; (2) changed the dosage and route of administration for the chemical abortion drugs; (3) reduced the number of required in-person office visits from three to one; (4) allowed non-doctors to prescribe and administer chemical abortions; (5) failed to require a clinical study to determine the safety of these changes to the chemical abortion drug regimen on pregnant girls under 18 years of age; and (6) eliminated the requirement for prescribers to report nonfatal adverse events from chemical abortion—thus ensuring that the FDA and the public would never learn of the dangers and injuries that would befall women and girls from removing these safeguards.

57. What is more, in 2021, the FDA announced that it would allow abortionists to dispense the chemical abortion drugs by mail or mail-order pharmacy—an action that a longstanding federal law independently and expressly prohibits.

58. Plaintiffs now ask this Court to protect women and girls by holding unlawful, setting aside, and vacating the FDA's actions to approve and eliminate the safeguards for those who take chemical abortion drugs.

II. The Chemical Abortion Regimen and Its Adverse Health Effects

59. The chemical abortion drug regimen requires the use of two drugs: (1) mifepristone (also known as "RU-486" and "Mifeprex") and (2) misoprostol.

60. As an endocrine disruptor, mifepristone is a synthetic steroid that blocks progesterone receptors in the uterus of a woman or girl. The hormone progesterone is necessary for the healthy growth of a baby and the maintenance of a pregnancy. When a woman or girl ingests the chemical abortion drug mifepristone, the drug blocks the action of the natural hormone progesterone, chemically destroys the baby's environment in the uterus, blocks nutrition to the baby, and ultimately starves the baby to death in the mother's womb.[10]

61. Because mifepristone alone works less than 25 percent of the time to complete the abortion, the FDA's chemical abortion drug regimen mandates the use

[10] *See* Ex. 4, Harrison Decl. at ¶ 21; Ex. 8, Skop Decl. at ¶ 10; Ex. 12, *The FDA and RU-486: Lowering the Standard for Women's Health: Hearing Before the Subcomm. on Crim. Just., Drug Pol'y, & Hum. Res. of the H. Comm. on Gov't Reform*, 109th Cong. 4 (2006).

of a second drug—misoprostol—to induce cramping and contractions in an attempt to expel the baby from the mother's womb.[11]

62. The only other FDA-approved use of misoprostol is to reduce the risk of gastric ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs) in patients at high risk of complications from gastric ulcers and patients at high risk of developing gastric ulceration.[12] Misoprostol's label warns that the drug "should not be taken by pregnant women to reduce the risk of ulcers" by NSAIDs.[13]

63. The use of these two chemical abortion drugs causes significant injuries and harms to pregnant women and girls.

64. For example, upwards of ten percent (10%) of women who take chemical abortion drugs will need follow-up medical treatment for an incomplete or failed chemical abortion,[14] with an average of thirty-nine percent (39%) of women requiring surgery if taken in the second trimester.[15]

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[11] *See* Ex. 4, Harrison Decl. at ¶ 21; Ex. 13, 2002 Citizen Petition of AAPLOG to FDA at 41 n.187 (Aug. 8, 2002); *see also* FDA-Approved Label for Mifepristone (Mifeprex) (Mar. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

[12] *See, e.g.,* Ex. 14, FDA-Approved Label for Misoprostol (Cytotec) (Jan. 2017), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019268s051lbl.pdf.

[13] *Id.*

[14] Ex. 18, Maarit Niinimaki et al., *Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study*, BJM, April 20, 2011, at 4.

[15] Ex. 15, Maarit J. Mentula et al., *Immediate adverse events after second trimester medical termination of pregnancy: results of a nationwide registry study*, 26 Hum. Reprod. 927, 931 (2011).

65. Twenty percent (20%) of females will have an adverse event after taking chemical abortion drugs—a rate four times higher than with surgical abortion. This includes over fifteen percent (15%) of females experiencing hemorrhaging and two percent (2%) having an infection during or after taking chemical abortion drugs.[16]

66. Chemical abortions are over fifty percent (50%) more likely than surgical abortions to result in an emergency department visit within thirty days, affecting one in twenty females.[17]

67. The number of chemical abortion-related emergency room visits increased by over five hundred percent (500%) between 2002 and 2015.[18]

68. For those women and girls who take chemical abortion drugs, there is a significant increase in risk of complications as the baby's gestational age increases. One study found that, after nine weeks' gestation, almost four times as many women and girls experience an incomplete abortion, nearly twice as many suffer an infection, and over six times as many women and girls require surgical abortion after consuming the chemical abortion drugs.[19]

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[16] Ex. 16, Maarit Niinimaki et al., *Immediate complications after medical compared with surgical termination of pregnancy*, 114 Obstetrics & Gynecology 795 (2009).

[17] Ex. 17, James Studnicki et al., *A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions*, *1999-2015*, Health Serv. Rsch. & Managerial Epidemiology, Nov. 9, 2021.

[18] *Id* at 5.

[19] Ex. 18, Niinimaki, *supra* note 14, at 5.

69. Chemical abortion drugs have heightened risks for women and girls with certain blood types. In fact, if a woman or girl with a Rh-negative blood type is not administered certain medication (Rhogam) at the time of her chemical abortion, she could experience isoimmunization, which threatens her ability to have future successful pregnancies. If an Rh-negative woman or girl is left untreated, her future baby will have a fourteen percent (14%) chance of being stillborn and a fifty percent (50%) chance of being born alive but suffering neonatal death or brain injury. Around fifteen percent (15%) of the U.S. population is at risk of this blood condition.[20]

70. Some abortion activists encourage women to lie to an emergency department doctor by saying they are having a miscarriage if they suffer complications requiring urgent care.[21] If a chemical abortion is miscoded as a miscarriage in the emergency room (which occurred sixty percent (60%) of the time in one study), the treating doctor's lack of knowledge results in the woman or girl

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[20] Ingrid Skop, *The Evolution of "Self-Managed" Abortion: Does the Safety of Women Seeking Abortion Even Matter Anymore?*, Charlotte Lozier Institute (Mar. 1, 2022), https://lozierinstitute.org/the-evolution-of-self-managed-abortion/.

[21] *See, e.g., Will a doctor be able to tell if you've taken abortion pills?*, Women Help Women (Sept. 23, 2019), https://womenhelp.org/en/page/1093/will-a-doctor-be-able-to-tell-if-you-ve-taken-abortion-pills; *How do you know if you have complications and what should you do?*, AidAccess, https://aidaccess.org/en/page/459/how-do-you-know-if-you-have-complications-and-what-should-you-do (last visited Nov. 14, 2022).

being at significantly greater risk of needing multiple hospitalizations and follow-up surgery.[22]

71. The risk of chemical abortions is not only physical: women and girls have described that their chemical abortion experiences harmed their mental health and left them feeling unprepared, silenced, regretful, or left with no other choice before undergoing a chemical abortion.[23]

72. Abortionists exacerbate this harm to a woman's or girl's mental health by not adequately informing her about what she will see when she self-administers chemical abortion drugs at home or in a hotel. For example, one woman was surprised and saddened to see that her aborted baby "had a head, hands, and legs" with "[d]efined fingers and toes."[24]

73. Given the FDA's refusal to require an ultrasound, abortionists can egregiously misdate the gestational age of a baby with devastating consequences. One young woman has alleged that she did not receive an ultrasound or any other physical examination to determine her baby's gestational age prior to receiving

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[22] Ex. 19, James Studnicki et al., *A Post Hoc Exploratory Analysis: Induced Abortion Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization*, Health Servs. Rsch. & Managerial Epidemiology, May 20, 2022.

[23] Ex. 20, Katherine A. Rafferty & Tessa Longbons, *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives*, 36 Health Commc'n 1485 (2021).

[24] Caroline Kitchener, *Covert network provides pills for thousands of abortions in U.S. post Roe*, Wash. Post: Politics (Oct. 18, 2022, 6:00 am), https://www.washingtonpost.com/politics/2022/10/18/illegal-abortion-pill-network/.

chemical abortion drugs from Planned Parenthood.[25] The abortionist misdated the baby's gestational age as six weeks, resulting in the at-home delivery of a "lifeless, fully-formed baby in the toilet," later determined to be around *30-36 weeks old*.[26] Because of this chemical abortion, the woman alleges that she "has endured significant stress, trauma, emotional anguish, physical pain, including laceration and an accelerated labor and delivery unaided by medication, lactation, soreness, and bleeding."[27]

III. The FDA's Authority to Review, Approve, or Deny New Drug Applications

74. The FDA's approval of new drugs must comply with federal laws and regulations that directly govern the agency, in addition to other laws that broadly govern the federal government's actions. Specifically, the FDA must comply with the Federal Food, Drug, and Cosmetic Act (FFDCA), the Pediatric Research Equity Act of 2003 (PREA), and the agency's regulations. When taking regulatory action on new drugs, the FDA must also meet the requirements of other federal laws restricting the distribution of certain drugs.[28]

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[25] Complaint at 9, *Doe v. Shah*, No. 501531/2021, (Sup. Ct. of N.Y., Cnty. of Kings Jan. 20, 2021), https://www.liveaction.org/news/wp-content/uploads/2022/10/Kings-Co-501531_2021_JANE_DOE_v_MEERA_SHAH.pdf.

[26] *Id.* at 10–11.

[27] *Id.* at 11.

[28] For a general overview of the FDA's drug approval process, *see How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, Congressional Research Service (May 8, 2018), https://crsreports.congress.gov/product/pdf/R/R41983.

A. New Drug Applications Under the Federal Food, Drug, and Cosmetic Act

75. Under the FFDCA, anyone seeking to introduce into commerce and distribute any new drug in the United States must first obtain the FDA's approval by filing a new drug application (NDA). 21 U.S.C. § 355(a).

76. A drug may be considered "new" by reason of the "newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 21 C.F.R. § 310.3(h)(4). A drug may also be considered "new" by reason of the "newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug . . . is not a new drug." *Id.* § 310.3(h)(5).

77. The NDA must contain extensive scientific data showing the safety and effectiveness of the drug. 21 U.S.C. § 355(d); 21 C.F.R. § 314.125.

78. Under the FFDCA, the FDA must reject an application if the clinical investigations "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)(2).

79. The FDA must also reject an application if "the results of such tests show that such drug is unsafe for use under such conditions or do not show that

such drug is safe for use under such conditions." 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)(3).

80. The FDA shall refuse an application if, based upon information submitted to the agency or upon the basis of any other information before the agency, the FDA "has insufficient information to determine whether such drug is safe for use under such conditions." 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)(4).

81. Finally, the FDA must deny an application if "there is a lack of substantial evidence that the new drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)(5).

82. The FFDCA defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U.S.C. § 355(d).

83. If a sponsor of an approved drug subsequently seeks to change the labeling, market a new dosage or strength of the drug, or change the way it manufactures a drug, the company must submit a supplemental new drug

application (sNDA) seeking the FDA's approval of such changes. 21 U.S.C. § 355(b); 21 C.F.R. §§ 314.54, 314.70.

84. Only the sponsor "may submit a supplement to an application." 21 C.F.R. § 314.71(a).

85. "All procedures and actions that apply to an application under [21 C.F.R.] § 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change." 21 C.F.R. § 314.71(b); *see also* 21 C.F.R. § 314.54(a) ("application need contain only that information needed to support the modification(s) of the listed drug").

86. The sNDA must also show that the drug is safe and effective for "the conditions of use prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. § 355(d).

87. The FFDCA allows a generic drug manufacturer to submit an abbreviated new drug application (ANDA) for approval to introduce into commerce and distribute a generic version of an approved drug. 21 U.S.C. § 355(j).

88. In the ANDA, the generic drug manufacturer must show, among other things, that (a) the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed and (b) the drug product is chemically the same as the already approved drug, allowing it to rely on the FDA's previous finding of safety and effectiveness for the approved drug. The route of administration, dosage form, and strength must also be the same. 21 U.S.C. § 355(j); 21 C.F.R. § 314.94.

B. Assessments on Pediatric Populations

89. In 1998, the FDA issued a regulation, called the Pediatric Rule, requiring an assessment specifically powered to determine the safety and effectiveness of a new drug on pediatric patients.[29] This rule allowed for full or partial waivers of its pediatric assessment requirements, set forth under then 21 C.F.R. § 314.55(c).

90. A federal district court subsequently held that the FDA had exceeded its statutory authority when issuing the Pediatric Rule and thus enjoined the FDA from enforcing the regulation. *See Ass'n of Am. Physicians & Surgeons v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002).

91. In response, President George W. Bush and Congress enacted PREA to codify the Pediatric Rule legislatively. This law expressly requires studies on the safety and effectiveness of drugs intended for pediatric populations, unless certain exceptions apply. The FDA may require an assessment on the drug's safety and effectiveness, extrapolate findings from studies on adult populations, or waive the assessment for pediatric populations. 21 U.S.C. § 355c.

92. In general, PREA requires an application or supplement to an application for a drug to include an assessment on the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations. 21 U.S.C. § 355c(a)(2)(A)(i). This assessment must also support dosing and

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[29] Ex. 21, Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (Dec. 2, 1998).

administration for each pediatric subpopulation for which the drug is safe and effective. 21 U.S.C. § 355c(a)(2)(A)(ii).

93. Under limited circumstances, PREA allows the FDA to avoid this assessment and, instead, extrapolate the safety and effectiveness of a drug for pediatric populations: "If the course of the *disease* and the effects of the drug are sufficiently similar in adults and pediatric patients, the [FDA] may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients." 21 U.S.C. § 355c(2)(B)(i) (emphasis added).

94. To support this extrapolation, the FDA must include "brief documentation of the scientific data supporting the conclusion" that the course of the *disease* and the effects of the drug are sufficiently similar in adults and pediatric patients. 21 U.S.C. § 355c(B)(iii) (emphasis added).

95. In addition, PREA also allows the FDA to grant a full or partial waiver of the requirement for pediatric assessments or reports on the investigation for a drug if one of the following situations exists: (1) "necessary studies are impossible or highly impracticable"; (2) "there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups"; or (3) the drug "does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients" and it "is not likely to be used in a substantial number of pediatric patients." 21 U.S.C. § 355c(a)(5)(A), (B).

96. PREA also deemed a waiver or deferral issued under the Pediatric Rule between April 1, 1999, and December 3, 2003, to be a waiver or deferral under 21 U.S.C. § 355c(a). 21 U.S.C. § 355c note.

C. Subpart H Regulations for Accelerated Approval of Certain New Drugs for Serious and Life-Threatening Illnesses

97. Both the FFDCA and PREA serve as the primary laws governing the FDA's review and approval of new drugs. The FDA has also implemented certain regulations to effectuate its legal obligations under these laws and to address certain public health crises over the years.

98. For example, on December 11, 1992, the FDA published the final rule, "New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval."[30]

99. This final rule established procedures "under which FDA will accelerate approval of certain new drugs and biological products for *serious or life-threatening illnesses*, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs."[31]

100. The FDA intended these procedures "to provide expedited marketing of drugs for patients suffering from *such illnesses* when the drugs provide a *meaningful therapeutic advantage* over existing treatment."[32]

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[30] Ex. 22, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992).

[31] *Id.* (emphasis added).

[32] *Id.* (emphasis added).

101. As codified under Subpart H, the FDA defined the scope of the new regulations:

> This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating *serious or life-threatening illnesses* and that provide *meaningful therapeutic benefit* to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

21 C.F.R. § 314.500 (emphasis added).

102. If the FDA's review under Subpart H concludes that a drug is effective but can be safely used *only if* distribution or use is restricted, the agency must "require such postmarketing restrictions as are needed to assure safe use of the drug product." 21 C.F.R. § 314.520(a).

103. Such restrictions may include distribution (1) "restricted to certain facilities or physicians with special training or experience" or (2) "conditioned on the performance of specified medical procedures." 21 C.F.R. § 314.520(a)(1), (2).

104. The limitations must "be commensurate with the specific safety concerns presented by the drug product." 21 C.F.R. § 314.520(b).

105. Under 21 C.F.R. § 314.530, the FDA may withdraw approval of drugs approved under Section 314.520 if:

> (1) A postmarketing clinical study fails to verify clinical benefit;
>
> (2) The applicant fails to perform a required postmarketing study with due diligence;
>
> (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;
>
> (4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

106. The FDA's preamble to the Subpart H rulemaking stated that "[t]he burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed."[33]

107. The *only* way the FDA can terminate an applicant's Subpart H restrictions is to notify the applicant that "the restrictions . . . no longer apply" because the "FDA [has] determine[d] that safe use of the drug product can be assured through appropriate labeling." 21 C.F.R. § 314.560.

D. Drugs Approved with Previous Subpart H Restrictions Deemed to Have Risk Evaluation and Mitigation Strategies

108. Congress decided to codify into law the FDA's postmarketing regulations under Subpart H when it enacted the Food and Drug Administration Amendments Act of 2007 (FDAAA) and created a new section of the FFDCA under 21 U.S.C. § 355-1. This new section authorizes the FDA to require persons submitting certain new drug applications to submit and implement a risk evaluation and mitigation strategy (REMS) if the FDA determines that a REMS is "necessary to ensure that the benefits of a drug outweigh the risks of the drug." 21 U.S.C. § 355-1(a).

109. Section 909(b)(1) of the FDAAA specified that a "drug that was approved before the effective date of this Act is . . . deemed to have in effect an

[33] Ex. 22, 57 Fed. Reg. at 58,952.

approved [REMS] . . . if there are in effect on the effective date of this Act elements to assure safe use [pursuant to Subpart H, 21 C.F.R. § 514.520]." H.R. 3580, 110th Cong. (2007). Thus, if the FDA previously attached postmarketing restrictions on a drug approved under Subpart H, the FDAAA converted those restrictions into a REMS.

110. Under the FDAAA, to allow safe access to drugs with known serious risks, the FDA may require that the REMS "include such elements as are necessary to assure safe use of the drug, because of its inherent toxicity or potential harmfulness" if the agency determines that the drug "is associated with a serious adverse drug experience." 21 U.S.C. § 355-1(f)(1).

111. These "Elements to Assure Safe Use" (ETASU) may require (1) prescribers of the drug "have particular training or experience" or be "specially certified," (2) practitioners or health care settings that dispense the drug be "specially certified," (3) doctors dispense the drug to patients "only in certain health care settings, such as hospitals," (4) doctors dispense the drug to patients "with evidence or other documentation of safe-use conditions, such as laboratory test results," (5) each patient be subject to "certain monitoring," and (6) each patient be enrolled in a "registry." 21 U.S.C. § 355-1(f)(3).

112. The FDA may also require an applicant to monitor and evaluate implementation of the REMS, in addition to working to improve those elements. 21 U.S.C. § 355-1(g).

113. The FDA may also include a communication plan to health care providers as part of the REMS to disseminate certain information about the drug and its risks. 21 U.S.C. § 355-1(e)(3).

114. An applicant "may propose the addition, modification, or removal of [the REMS] . . . and shall include an adequate rationale to support such proposed addition, modification, or removal." 21 U.S.C. § 355-1(g)(4)(A).

IV. Federal Laws Restrict Distribution of Chemical Abortion Drugs

115. Two federal laws restrict the distribution of abortion-inducing drugs. 18 U.S.C. §§ 1461–62. These laws apply to both upstream and downstream distribution.

116. *First*, 18 U.S.C. § 1461 prohibits the use of postal "mails" to convey or deliver chemical abortion drugs. Specifically, it prohibits the mailing or delivery by any letter carrier of "[e]very article or thing designed, adapted, or intended for producing abortion" and "[e]very article, instrument, substance, drug, medicine, or thing, which is advertised or described in a manner calculated to lead to another to use or apply it for producing abortion."

117. *Second*, 18 U.S.C. § 1462 broadly prohibits the use of "any express company or other common carrier" to transport abortion drugs in interstate or foreign commerce. Specifically, it prohibits the use of any express company or common carrier to distribute "any drug, medicine, article, or thing designed, adapted, or intended for producing abortion."

V. The FDA's Review of the Population Council's Application to Market Chemical Abortion Drugs in the United States

118. The French pharmaceutical company Roussel Uclaf S.A. first developed and tested mifepristone under the name RU-486. By April 1990, the drug had become fully available in France.[34]

119. But Roussel Uclaf's German parent company, Hoechst AG, prohibited the drug manufacturer from attempting to enter the U.S. market and filing a new drug application with the FDA.[35] Hoechst's resistance and desire to keep a low profile was due, in part, to its corporate history and complicity in previous mass genocide.[36]

120. Nevertheless, on January 22, 1993—his second full day in office—President Bill Clinton directed then-HHS Secretary Donna Shalala to assess initiatives to promote the testing and licensing of RU-486 in the United States.[37]

121. According to a Roussel Uclaf official, President Clinton also wrote to Hoechst asking the company to file a new drug application with the FDA, which Hoechst refused to do.[38]

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[34] Ex. 13, 2002 Citizen Petition at 7–8.

[35] *Id* at 8.

[36] Julie A. Hogan, *The Life of the Abortion Pill in the United States*, at 23–24 (2000), http://nrs.harvard.edu/urn-3:HUL.InstRepos:8852153 ("Hoechst traces its corporate history to I.G. Farben, the manufacturer of Zyklon-B, which was used in the gas chambers of Auschwitz," and therefore "did not want to be credited with doing to fetuses what the Nazis had done to the Jews.").

[37] Ex. 13, 2002 Citizen Petition at 8.

[38] *Id.*

122. In early 1993, as HHS later reported, Secretary Shalala and then-FDA Commissioner David Kessler likewise "communicated with senior Roussel Uclaf officials to begin efforts to pave the way for bringing RU-486 into the American marketplace."[39]

123. Specifically, according to HHS, "[i]n April 1993, representatives of FDA, Roussel Uclaf and the Population Council, a not-for-profit organization, met to discuss U.S. clinical trials and licensing of RU-486." Between April 1993 and May 1994, the parties continued their negotiations.[40]

124. "The Population Council is a nonprofit founded in 1952 by John D. Rockefeller III to address supposed world overpopulation. . . . [Rockefeller] served as the organization's first president."[41]

125. The talks between the FDA, the Population Council, and Roussel Uclaf culminated in what HHS called a "donation": Roussel Uclaf transferred, "without remuneration, its United States patent rights to mifepristone (RU-486) to the Population Council."[42]

126. After obtaining the American patent rights to mifepristone, the Population Council conducted clinical trials in the United States.[43]

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[39] *Id.* (quoting HHS Fact Sheet, *Mifepristone (RU-486): Brief Overview* (May 16, 1994)).

[40] HHS Fact Sheet, *Mifepristone (RU-486): Brief Overview*.

[41] Population Council, https://www.influencewatch.org/non-profit/population-council/ (last visited Nov. 15, 2022).

[42] Ex. 13, 2002 Citizen Petition at 8–9 (quoting HHS Press Release, *Roussel Uclaf Donates U.S. Patent Rights for RU-486 to Population Council*, (May 16, 1994)).

[43] *Id.* at 9.

127. The Population Council then filed a new drug application for "mifepristone 200 mg tablets" on March 18, 1996.[44]

128. The FDA initially accorded the drug standard review; but in a May 7, 1996, letter, the FDA's Center for Drug Evaluation and Research notified the Population Council that mifepristone would receive priority review.[45]

129. On September 18, 1996, the FDA issued a letter stating that the application was "approvable" and requested more information from the Population Council.[46]

130. On February 18, 2000, the FDA issued a second "approvable" letter, setting forth the remaining prerequisites for approval. This letter announced that the FDA had "considered this application under the restricted distribution regulations contained in 21 C.F.R. § 314.500 (Subpart H) and [had] concluded that restrictions as per [21] CFR § 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[47]

131. The FDA told the Population Council that the agency would proceed under Subpart H because the FDA "concluded that adequate information has not been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for use as recommended."[48]

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[44] *Id.* at 10.
[45] *Id.*
[46] *Id.* at 10–11.
[47] Ex. 23, FDA Letter to Population Council re: NDA (Feb. 18, 2000) at 5.
[48] *Id.*

132. Given the known dangers of chemical abortion drugs, the FDA needed to approve the Population Council's application under Subpart H because this regulatory authority provided the FDA with the *only* means to restrict the drugs' distribution and use "to assure safe use." 21 C.F.R. 314.520.

133. In response to the proposed Subpart H consideration, the Population Council objected and explained that its application for mifepristone did not fall within the scope of Subpart H.[49]

134. The Population Council thus wrote a letter to the FDA just three weeks before the final approval of mifepristone, arguing that "it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider."[50]

135. The Population Council stated that "[n]either pregnancy nor unwanted pregnancy is an illness, and Subpart H is therefore inapplicable for that reason alone."[51]

136. Moreover, as the Population Council observed, "[n]either is pregnancy nor unwanted pregnancy a 'serious' or 'life-threatening' situation as that term is defined in Subpart H."[52]

137. And after quoting the preamble to the FDA's Subpart H Final Rule, the Population Council's letter stated that "[t]he plain meaning of these terms does

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[49] Ex. 13, 2002 Citizen Petition at 20.
[50] *Id.*
[51] *Id.*
[52] *Id.*

not comprehend normal, everyday occurrences such as pregnancy and unwanted pregnancy."[53]

138. The letter added that unlike HIV infection, pulmonary tuberculosis, cancer, and other illnesses, "pregnancy and unwanted pregnancy do not affect survival or day-to-day functioning as those terms are used in Subpart H."[54]

139. The Population Council explained that "although a pregnancy 'progresses,'" the development of a pregnancy "is hardly the same as the worsening of a disease that physicians call progression."[55]

140. Despite these last-minute objections, the Population Council ultimately ceased its opposition to the FDA's intention to approve chemical abortion drugs under Subpart H on September 15, 2000.[56]

VI. The FDA's Approval of the Population Council's Application to Market Chemical Abortion Drugs in the United States.

141. On September 28, 2000, the FDA approved chemical abortion drugs under Subpart H "for the medical termination of intrauterine pregnancies through 49 days' pregnancy."[57]

142. The FDA informed the Population Council that Subpart H "applies when FDA concludes that a drug product shown to be effective can be safely used

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[53] *Id.*

[54] *Id.*

[55] *Id.*

[56] Ex. 24, 2000 FDA Approval Memo. to Population Council re: NDA 20-687 Mifeprex (mifepristone) at 6 (Sept. 28, 2000).

[57] Ex. 25, 2000 FDA Approval Letter for Mifeprex (mifepristone) Tablets at 1 (Sept. 28, 2000).

only if distribution or use is restricted, such as to certain physicians with certain skills or experience."[58]

143. The FDA would not have been able to approve the chemical abortion drugs without invoking Subpart H, as it was the only authority available to the agency to allow it to apply postmarketing restrictions on the drugs.[59]

144. To defend its use of Subpart H, the FDA agency declared that "the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H" and asserted that "[t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure."[60]

145. The FDA stated that the chemical abortion drugs' "labeling is now part of a total risk management program." In particular, "[t]he professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement will together constitute the approved product labeling to ensure any future generic drug manufacturers will have the same risk management program."[61]

146. The 2000 approval required the Population Council to include on the drugs' label a "black box warning for special problems, particularly those that may lead to death or serious injury."[62]

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[58] Ex. 24, 2000 FDA Approval Memo. at 6.

[59] Ex. 26, 2003 Citizen Petitioners' Response to Opposition Comments filed by The Population Council, Inc. and Danco Laboratories, LLC to Comments at 2–4 (Oct. 10, 2003) https://www.aaplog.org/wp-content/uploads/2002/08/ResponseToDanco10-03reRU-486.pdf (2003 Response).

[60] Ex. 24, 2000 Approval Memo. at 6.

[61] *Id.* at 2.

[62] *Id.*

147. The approved regimen in 2000 contained measures to assure safe use, including requiring at least three office visits: (1) the Day 1 in-person dispensing and administration of mifepristone; (2) the Day 3 in-person dispensing and administration of misoprostol; and (3) the Day 14 return to the doctor's office to confirm no fetal parts or tissue remain.[63]

148. The FDA explained that "[r]eturning to the health care provider on Day 3 for misoprostol . . . assures that the misoprostol is correctly administered," and it "has the additional advantage of contact between the patient and health care provider to provide ongoing care, and to reinforce the need to return on Day 14 to confirm that expulsion has occurred."[64]

149. The FDA's Subpart H restrictions included the following requirements for abortionists: the ability to assess the duration of pregnancy accurately and to diagnose ectopic pregnancies (chemical abortion drugs cannot end an ectopic pregnancy, but the symptoms of these drugs resemble hemorrhaging from a life-threatening ectopic pregnancy[65]); the requirement to report any hospitalization, transfusion, or other serious events; and the ability to provide surgical intervention or to ensure that the patient has access to other qualified physicians or medical facilities.[66]

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[63] *Id.* at 2–3.

[64] *Id.* at 3.

[65] Ex. 8, Skop Decl. ¶ 29; *AAPLOG Statement on FDA removing Mifepristone safety protocols (REMS)*, at 2, https://aaplog.org/wp-content/uploads/2021/04/AAPLOG-Statement-on-FDA-removing-mifepristone-REMS-April-2021-1.pdf.

[66] Ex. 24, 2000 Approval Memo. at 6.

150. The FDA's restrictions on the distribution of mifepristone included:

- In-person dispensing from the doctor to the woman or girl;
- Secure shipping procedures;
- Tracking system ability;
- Use of authorized distributors and agents; and
- Provision of the drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing.[67]

151. The FDA did not include prohibitions on the upstream distribution of the chemical abortion drugs—from the manufacturer or importer to the abortionist—by mail, express company, or common carrier as proscribed by federal laws, nor did the FDA acknowledge and address these laws.[68]

152. The FDA also outlined the Population Council's two post-approval study commitments.[69] The Population Council was to conduct "a monitoring study to ensure providers who did not have surgical-intervention skills and referred patients for surgery had similar patient outcomes as those patients under the care of physicians who possessed surgical skills (such as those in the clinical trial)."[70]

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[67] *Id.*

[68] *Id.*

[69] Ex. 25, 2000 Approval Letter at 2–3.

[70] Ex. 24, 2000 Approval Memo. at 7.

The Population Council also agreed "to study ongoing pregnancies and their outcomes through a surveillance, reporting, and tracking system."[71]

153. In the 2000 Approval, the FDA informed the Population Council that the agency was "waiving the pediatric study requirement for this action on this application."[72] Without explanation of the effects of chemical abortion drugs on puberty or substantiation of its decision, the FDA asserted that "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen." [73]

154. The FDA nonetheless highlighted the findings of one limited study that included 51 subjects under 20 years of age. The agency explained that the approved labeling states that the safety and efficacy for girls under 18 years of age "have not been studied" because the raw data from this limited study had not been submitted for review, the pediatric population was not part of the NDA indication, the data on safety and effectiveness were only reviewed for the indication's age group (18–35 years of age), and the clinical trials excluded patients younger than 18 years old.[74]

155. The FDA believed it would eventually overcome this data deficiency because the Population Council would "collect outcomes in their [post-approval]

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[71] *Id.*
[72] Ex. 25, 2000 Approval Letter at 3.
[73] Ex. 24, 2000 Approval Memo. at 7.
[74] *Id.*

studies of women of all ages to further study this issue"[75]—even though those studies were not designed to evaluate the safety and effectiveness of mifepristone on girls under the age of 18 years.

156. But the FDA released the Population Council from its obligation to conduct these studies in 2008.[76]

157. Therefore, since the 2000 Approval, the FDA has continued to allow pregnant girls of *any age* to take chemical abortion drugs—despite never requiring a study specifically designed to determine the safety and effectiveness of these drugs.

158. With the FDA approval in hand, the Population Council then granted Danco Laboratories, LLC ("Danco"), which was incorporated in the Cayman Islands in 1995, an exclusive license to manufacture, market, and distribute Mifeprex in the United States.[77]

VII. 2002 Citizen Petition

159. The FDA's regulations prohibit a litigant from going straight to court to challenge the agency's approval of a new drug. Instead, the FDA's regulations require the submission of a "citizen petition" requesting the agency take or refrain from taking any form of administration action before filing a lawsuit. 21 C.F.R. §§ 10.30, 10.45(b). These regulations allow the FDA to indefinitely delay a final response to a citizen petition. 21 C.F.R. § 10.30(e)(2)(iv). The FDA's eventual

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[75] *Id.*

[76] Ex. 27, 2016 FDA Letter to AAPLOG, Christian Medical & Dental Associations, and Concerned Women for America denying 2002 Citizen Petition, Docket No. FDA-2002-P-0364, at 31 (Mar. 29, 2016) (2016 Petition Denial).

[77] Ex. 13, 2002 Citizen Petition at 9.

decision on a citizen petition constitutes a final agency action for the underlying FDA action and the related citizen petition, and both are reviewable in the courts under the APA. 21 C.F.R. § 10.45(c).

160. In August 2002, Plaintiffs AAPLOG and Christian Medical & Dental Associations, along with the Concerned Women for America, (collectively, 2002 Petitioners), submitted a citizen petition (2002 Citizen Petition) with the FDA pursuant to 21 C.F.R. §§ 10.30 and 10.35; 21 C.F.R. Part 314, Subpart H (§§ 314.500–314.560); and Section 505 of the FFDCA (21 U.S.C. § 355).[78]

161. The 2002 Petitioners requested that the FDA impose an immediate stay of the approval of mifepristone and ultimately revoke the approval, in addition to requesting a full FDA audit of the underlying clinical studies.[79]

162. The 2002 Petitioners stated that the FDA's approval of mifepristone in 2000 violated the APA for many reasons, including because it was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law, given that (1) the FDA lacked the authority to approve mifepristone under Subpart H and (2) the FDA incorporated misoprostol as part of the chemical abortion regimen despite not receiving an sNDA for this new use of the drug.[80]

163. The 2002 Petitioners explained how the 2000 Approval violated Subpart H because pregnancy, without major complications, is not a "serious or life-threatening illness" for purposes of this accelerated approval authority. "Thus,

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[78] *Id.* at 1.

[79] *Id.*

[80] *Id.* at 18–23, 41–48.

pregnancy is not the kind of exceptional circumstance that falls within the scope of Subpart H. The fact that the Mifeprex Regimen is intended for healthy women provides further evidence of this point."[81]

164. Moreover, "there is a less dangerous, more effective alternative to Mifeprex available for the termination of pregnancies: namely, surgical abortions." Nor does mifepristone "treat a subset of the female population that is unresponsive to, or intolerant of surgical abortion." Indeed, as the 2000 Mifeprex label acknowledged, because "medical abortion failures should be managed with surgical termination," the option for surgical abortion must be available for any woman or girl who undergoes chemical abortion.[82]

165. Nor did the clinical trials compare chemical abortion with the existing "therapy," surgical abortion, to support a finding of a "meaningful therapeutic benefit over existing treatments."[83]

166. The 2002 Petitioners also pointed out that the clinical trials that the Population Council submitted to support its NDA failed to present "substantial evidence" that the mifepristone regimen is safe and effective.[84]

167. In fact, as the 2002 Citizen Petition demonstrated, the FDA's 2000 Approval has endangered women's lives because it lacked the necessary safeguards for this dangerous regimen. For instance, the FDA failed to require an ultrasound,

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[81] *Id.* at 19.
[82] *Id.* at 21–22.
[83] *Id.* at 37.
[84] *Id.* at 24–41.

which is necessary both to determine an accurate gestational age of the baby and to rule out an ectopic pregnancy. The FDA also did not restrict the regimen to physicians who have received proper training and possess admitting privileges to emergency facilities. In light of the FDA's subsequent acknowledgment that women had serious adverse events since the 2000 Approval, the 2002 Citizen Petition urged the FDA to "react to these sentinel events because the clinical trials underlying the approval of the Mifeprex Regimen did not adhere to FDA's endorsed scientific methodology for such trials."[85]

168. What is more, the 2002 Petitioners challenged the 2000 Approval because the U.S. clinical trial for mifepristone did not mirror the anticipated conditions of use under the approved label despite the FFDCA's requirements under 21 U.S.C. § 355(d). Under the conditions of the U.S. clinical trial:

(a) the investigators relied on transvaginal ultrasonography (along with menstrual history and pelvic examination) to confirm the gestational age of each pregnancy and exclude women with ectopic pregnancies;

(b) the physicians had experience in performing surgical abortions, were trained in the administration of the mifepristone-misoprostol procedure, and had admitting privileges at medical facilities that could provide emergency care and hospitalization; and

[85] *Id.* at 49–71.

(c) all patients needed to be within one hour of emergency facilities or the facilities of the principal investigator; and

(d) women were monitored for four hours for adverse events after taking misoprostol.[86]

169. Because the FDA's 2000 Approval did not require these safeguards for women and girls using chemical abortion drugs, the 2002 Petitioners reasoned that the agency should not have extrapolated conclusions about the safety and effectiveness of chemical abortion drugs under the approved label.[87]

170. The 2002 Citizen Petition also requested that the FDA withdraw the 2000 Approval of the chemical abortion drugs because the sponsor had not been enforcing the limited restrictions on the use of the drug regimen. Among the deviations from the approved regimen, physicians were offering chemical abortion drugs to women with pregnancies beyond the maximum seven weeks and eliminating the second of the three prescribed visits (i.e., in-facility administration of misoprostol).[88]

171. Subpart H authorizes the FDA to withdraw approval of a drug approved under Section 514.520 if "[t]he applicant fails to adhere to the postmarketing restrictions agreed upon." 21 C.F.R. § 314.530(a)(4). Because "the burden is on the applicant to ensure that the conditions of use under which the

[86] *Id.* at 75–76.
[87] *Id.* at 76.
[88] *Id.* at 71–75.

applicant's product was approved are being followed," the 2002 Petitioners asked the FDA to exercise its authority to withdraw its approval for mifepristone.[89]

172. The 2002 Petitioners also challenged the FDA's decision to waive the agency's regulatory requirement to conduct a pediatric study—the failure of which endangered the health and safety of girls—because it did not meet the requirements for such a waiver.[90]

173. The 2002 Citizen Petition next pointed out that the FDA impermissibly reduced the Population Councils' post-approval studies during the final stages of the FDA's review in 2000. "Not only did FDA approve the NDA on the basis of clinical trials so defective with respect to their design and execution as to render them insufficient to establish short-term safety and effectiveness, but FDA also permitted the Population Council to substantially pare down the [post-approval] trials that it would perform."[91]

174. Finally, the FDA then "compounded its failure to require the Population Council and Danco to comply with the strictures of the Pediatric Rule when it permitted them to consider the effect of the Mifeprex Regimen on patients under 18 as part of another study rather than as a separate [post-approval] study."[92] Because chemical abortion drugs "could conceivably interfere with

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[89] Ex. 13, 2002 Citizen Petition at 75.
[90] *Id.* at 76–83.
[91] *Id.* at 84–85.
[92] *Id.* at 86.

pubertal development," girls under 18 years of age deserve separate consideration in studies with significant numbers of participants.[93]

175. On October 10, 2003, the 2002 Petitioners filed a response ("2003 Response") to opposition comments by the Population Council and Danco. The 2003 Response not only responded to these comments, but it also provided the FDA with additional evidence that the safety and effectiveness of chemical abortion drugs have not been established in accordance with the requirements of the FFDCA or the FDA's own regulations.[94]

VIII. Implementation of a REMS for Mifepristone

176. After receiving the 2002 Citizen Petition, the FDA's next significant regulatory action on chemical abortion drugs involved incorporating Congress's mandate to convert Subpart H postmarketing restrictions for previously approved drugs into a REMS.

177. As previously discussed, Section 909(b)(1) of the FDAAA specified that a "drug that was approved before the effective date of this Act is . . . deemed to have in effect an approved [REMS] . . . if there are in effect on the effective date of this Act elements to assure safe use [pursuant to 21 C.F.R. § 514.520]."

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[93] *Id.* at 86, n. 377.

[94] Ex. 26, 2003 Response.

178. In a March 27, 2008, Federal Register notice, the FDA identified chemical abortion drugs as one of "those drugs that FDA has determined will be deemed to have in effect an approved REMS."[95]

179. In 2011, pursuant to the 2008 notice, the FDA approved a REMS for chemical abortion drugs in accordance with section 909(b)(1) of the FDAAA.[96]

180. The FDA "determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications."[97]

181. The REMS incorporated the previous Subpart H restrictions and consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.[98]

182. The REMS required "prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications."[99]

183. The FDA also instructed Danco that, "[a]s part of the approval under Subpart H, as required by 21 CFR § 314.550, you must submit all promotional

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[95] Ex. 28, Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16,313, 16,314 (Mar. 27, 2008).

[96] Ex. 29, 2011 FDA Supplemental Approval Letter to Danco Laboratories, LLC at 1 (June 6, 2011) (2011 Approval Letter).

[97] *Id.* at 1.

[98] *Id.* at 1; Ex. 30, 2011 REMS for NDA 20-687 Mifeprex (mifepristone) Tablets, 200mg (June 8, 2011) (2011 REMS).

[99] Ex. 29, 2011 Approval Letter at 1; Ex. 30, 2011 REMS.

materials, including promotional labeling as well as advertisements, at least 30 days before the intended time of initial distribution of the labeling or initial publication of the advertisement."[100]

IX. The FDA's Denial of the 2002 Citizen Petition

184. Almost *fourteen years* after receiving the 2002 Citizen Petition—on March 29, 2016—the FDA denied the 2002 Citizen Petition ("2016 Denial").[101]

185. The FDA abused its regulatory authority under 21 C.F.R. § 10.30(e)(2)(iv) to delay a final response to the 2002 Citizen Petition.

186. In the 2016 Denial, the FDA asserted that it appropriately approved chemical abortion drugs under Subpart H because "[a]s FDA made clear in the preamble to the final rule for subpart H, the subpart H regulations are intended to apply to serious or life-threatening *conditions*, as well as to illnesses or diseases."[102]

187. The FDA further asserted that the Subpart H premable "also made clear that a condition need not be serious or life-threatening in all populations or in all phases to fall within the scope of these regulations."[103]

188. The FDA asserted that "[u]nwanted pregnancy falls within the scope of subpart H under § 314.500 because unwanted pregnancy, like a number of illnesses

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[100] Ex. 29, 2011 Approval Letter at 2–3.
[101] Ex. 27, 2016 Petition Denial.
[102] *Id.* at 4 (emphasis added).
[103] *Id.*

or conditions, can be serious for certain populations or under certain circumstances."[104]

189. The FDA also asserted that chemical abortion "provides a meaningful therapeutic benefit to some patients over surgical abortion" because chemical abortion "provides an alternative to surgical abortion," which itself can lead to complications such as "a severe allergic reaction, a sudden drop in blood pressure with cardiorespiratory arrest, death, and a longer recovery time following the procedure."[105]

190. The FDA also asserted that the clinical trials constituted "substantial evidence" of effectiveness, while contending that the "FDA regulations do not require that a study be blinded, randomized, and/or concurrently controlled."[106]

191. The FDA then asserted that its decision not to require studies of pediatric patients "was consistent with FDA's implementation of the regulations in effect at that time." The agency also asserted that its 2000 Approval "determined that there were sufficient data from studies of mifepristone." Even though the 2000 Approval said the FDA was waiving the requirement for a pediatric assessment, the 2016 Petition Denial stated that the 2000 Approval "should have stated our conclusion that the pediatric study requirements were waived for pre-menarchal patients and that the pediatric study requirements were met for post-menarchal

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[104] *Id.*

[105] *Id.* at 5.

[106] *Id.* at 9.

pediatric patients, rather than stating that we were waiving the requirements for all pediatric groups."[107]

192. In response to the 2002 Citizen Petition's argument that the FDA's inclusion of misoprostol as part of the mifepristone regimen was illegal because the sponsor of that drug had not submitted an sNDA, the FDA asserted that "[n]either the FD&C Act nor FDA regulations require the submission of a supplemental NDA by the sponsor of the misoprostol NDA for the use of misoprostol as part of the approved treatment regimen for Mifeprex."[108]

193. The FDA provided "[e]xamples of approved drug labeling that refer to the concomitant use of another drug without there being a specific reference to the combined therapy in the previously approved labeling for the reference drug."[109] But the FDA did not purport to provide an example of drug labeling where that second drug was not approved for the use of the new indication.

X. The FDA's 2016 Major Changes to the Mifepristone Regimen

194. On the *same day* that the FDA denied the 2002 Citizen Petition—March 29, 2016—the FDA also approved major changes to the mifepristone regimen (2016 Major Changes) in response to an sNDA that Danco had submitted to the FDA on May 28, 2015.[110]

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[107] *Id.* at 29.

[108] *Id.* at 15.

[109] *Id.*

[110] Ex. 31, 2016 FDA Letter to Danco Laboratories re: NDA 020687, Supp 20 (Mar. 29, 2016).

195. The FDA acknowledged that the 2000 Approval hinged on necessary safeguards to protect women and girls from the dangers of chemical abortion drugs. The FDA's "Summary Review" of the 2016 Major Changes recalled that "[a]t the time of the September, 2000 approval, FDA restricted distribution of Mifeprex under 21 CFR 314.520." After summarizing the history and provisions of the REMS for mifepristone, the FDA noted that "[t]he REMS for Mifeprex incorporated the restrictions under which the drug was originally approved."[111] But the FDA decided to remove these crucial protections after reconsidering and reopening the 2000 Approval.

196. The FDA acknowledged that "these major changes are interrelated," demonstrating the agency's awareness that each change impacted the others.[112]

197. The 2016 Major Changes included the following revisions to the 2000 Approval's safeguards for women and girls:

(a) extending the maximum gestational age at which a woman or a girl can abort her baby from 49 days to 70 days;

(b) altering the mifepristone dosage from 600 mg to 200 mg, the misoprostol dosage from 400 mcg to 800 mcg, and misoprostol administration from oral to buccal (cheek pouch);

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[111] Ex. 32, FDA, Center for Drug Evaluation and Research, Summary Review of Application Number: 020687Orig1s020, at 4 (Mar. 29, 2016) (2016 Summary Review).

[112] *Id.* at 6.

(c) eliminating the requirement that administration of misoprostol occur in-clinic;

(d) broadening the window for misoprostol administration to include a range of 24-48 hours after taking mifepristone, instead of 48 hours afterwards;

(e) adding a repeat 800 mcg buccal dose of misoprostol in the event of an incomplete chemical abortion;

(f) removing the requirement for an in-person follow-up examination after an abortion; and

(g) allowing "healthcare providers" other than physicians to dispense and administer the chemical abortion drugs. [113]

198. Despite these major changes to the regimen, the FDA eliminated the requirement for prescribers to report all nonfatal serious adverse events from chemical abortion drugs. Rather than require future adverse event reports from abortionists about whether revising the dosages and removing the initial safeguards harmed women and girls, the FDA simply asserted that "after 15 years of reporting serious adverse events, the safety profile for Mifeprex is essentially unchanged." The FDA at least conceded that "[i]t is important that the Agency be informed of any deaths with Mifeprex to monitor new safety signals or trends."[114]

[113] *Id.* at 6–10.

[114] *Id.* at 27.

199. As with the 2000 Approval, the 2016 Major Changes did not include prohibitions on the upstream distribution of chemical abortion drugs by mail, express company, or common carrier as proscribed by federal laws, nor did the FDA acknowledge and address these laws.

A. The FDA's Evidence for the Safety and Effectiveness of the 2016 Major Changes

200. The FDA lacked substantial evidence that the 2016 Major Changes would have the effect it purported or was represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.

201. The FDA's review and approval did not include a single adequate and well-controlled investigation that evaluated the safety and effectiveness of mifepristone and misoprostol under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.

202. Instead, the FDA relied on studies that evaluated only one or just a few of the major changes that the FDA enacted in 2016; as the FDA acknowledged, "in some cases data from a given study were relied on to provide evidence to support multiple changes"[115]—but no study supported all the changes.

203. For example, the FDA relied on a study lead by a former longtime employee of the Population Council to support extending the maximum gestational age to 70 days, changing the dosing regimen, and authorizing a repeat dose of

[115] Ex. 32, 2016 Summary Review at 6.

misoprostol if the first dose fails.[116] In this study, the abortionists (1) confirmed gestational age (and presumably screened for ectopic pregnancies) "based on routine ultrasound practices," (2) required the study participants to return to the study site 7 to 14 days after using mifepristone "for clinical assessment, which included ultrasonography," and (3) "intervened surgically if they deemed it medically necessary or at the patient's request."[117] But the labeling that the FDA approved with the 2016 Major Changes did not require (1) an ultrasound to confirm gestational age or screen for an ectopic pregnancy, (2) an in-person follow-up exam using ultrasonography, and (3) an ability of abortionists to personally perform surgical abortion if necessary. Such variations between the study conditions and the approved labeling fail to comply with the requirements of the FFDCA.

204. Moreover, the studies on which the FDA relied for each individual major change all contained at least one fatal flaw, including the following substantial weaknesses: significant loss to follow-up; safeguards not required under the labeling; small sample size lacking statistical significance; not powered to evaluate safety; and bias.

205. In fact, many of these studies showed that the new chemical abortion regimen was *unsafe* for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof, or they failed to show that chemical abortion was safe under such conditions.

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[116] Ex. 33, Beverly Winikoff et al., *Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age*, 120 Obstetrics & Gynecology 1070 (2012).
[117] *Id.* at 1071.

B. The FDA's Lack of Research on Pediatric Populations for the 2016 Major Changes

206. The FDA's 2016 Major Changes continued to allow pregnant girls of any age to use chemical abortion drugs—despite not knowing whether these dangerous drugs could have an adverse impact on the health, safety, and welfare of developing girls.

207. The FDA did not require Danco to submit an assessment on the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, nor did the FDA require Danco to submit an assessment that supported the dosing and administration for each pediatric subpopulation for which the drug is safe and effective.[118]

208. The FDA "granted a partial PREA waiver for pre-menarcheal females ages birth to 12 years because it would be impossible to conduct studies in this pediatric population, as pregnancy does not exist in premenarchal females." The FDA then concluded that Danco "fulfilled the remaining PREA requirement in postmenarcheal females by submitting published studies of Mifeprex for pregnancy termination in postmenarcheal females less than 17 years old." The FDA cited three published studies in support of this conclusion.[119]

209. The primary study on which the FDA relied, *Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days*, by Mary Gatter and Deborah Nucatola of Planned Parenthood of Los Angeles and

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[118] Ex. 32, 2016 Summary Review at 18–20.

[119] *Id.* at 18–19.

Kelly Cleland of Princeton University's Office of Population Research, evaluated the proposed dosing regimen followed by home administration of misoprostol through 63 days' gestation. The study also included postmenarcheal girls in the study population, from which the FDA extrapolated its conclusion.[120]

210. For the pediatric population under 18 years of age, the Planned Parenthood study stated that it had a loss to follow-up of twenty percent (20%). Therefore, the authors lacked any knowledge of whether these girls died, were hospitalized, or experienced other serious adverse events.[121] The authors also recognized that "[l]oss to follow-up was significantly higher among the *youngest* age group."[122]

211. The FDA minimized this significant data gap by asserting that "loss to follow-up was *slightly higher* in those less than 18 years old."[123] Despite this significant data gap, the FDA went on to conclude that "age did not adversely impact efficacy outcomes."[124]

212. Furthermore, in this study, Planned Parenthood also performed an ultrasound examination on *all* females prior to the chemical abortions, in addition to giving them "routine antibiotic coverage" at the beginning of the chemical

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[120] *Id.* at 19 (citing Ex. 34, Mary Gatter et al., *Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days*, 91 Contraception 269 (2015).

[121] Ex. 34, Gatter at 4–5.

[122] *Id.* (emphasis added).

[123] Ex. 32, 2016 Summary Review at 19 (emphasis added).

[124] *Id.*

abortion regimen.[125] But the FDA did not require any of these safeguards for women and girls under the 2016 Major Changes.

213. The FDA did not address or discount any potential conflict of interest or bias in the study—despite the study disclosing that Planned Parenthood Federation of America provided funding for the study. Nor did the FDA address or discount any potential conflict of interest or bias in the study even though its authors, Mary Gatter[126] and Deborah Nucatola,[127] had significant incentives to increase their income and Planned Parenthood's profits through abortion-related actions outside of performing surgical abortion.[128]

214. A second study that the FDA cited in support of its PREA conclusion was based on a nationwide registry of induced abortions and hospital register data in Finland.[129] For the adolescent cohort who had chemical abortions, the study

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[125] Ex. 34, Gatter at 2.

[126] *See, e.g.*, The Center for Medical Progress, *Second Planned Parenthood Senior Executive Haggles Over Body Parts Prices, Changes Abortion Methods*, YouTube (July 21, 2015), https://www.youtube.com/watch?v=MjCs_gvImyw (video capturing Gatter saying she "want[s] a Lamborghini" when discussing the price that she would charge for selling intact aborted fetal body parts).

[127] *See, e.g.,* The Center for Medical Progress, *Planned Parenthood Uses Partial-Birth Abortions to Sell Baby Parts*, YouTube (July 14, 2015), https://www.youtube.com/watch?v=jjxwVuozMnU (video capturing Nucatola stating that Planned Parenthood affiliates would be "happy" selling intact aborted fetal body parts for a "reasonable" price that is "a little better than break even").

[128] The Fifth Circuit has recognized the overall authenticity and veracity of the undercover videos capturing Planned Parenthood's desire to profit from the trafficking of aborted fetal body parts. *See Planned Parenthood of Greater Tex. Family Planning & Preventative Health Servs., Inc. v. Smith*, 913 F.3d 551, 559 n. 6 (5th Cir. 2019), *on reh'g en banc sub nom. Planned Parenthood of Greater Tex. Fam. Plan. & Preventative Health Servs., Inc. v. Kauffman*, 981 F.3d 347 (5th Cir. 2020).

[129] Ex. 32 2016 Summary Review at 19–20 (citing Ex. 18, Niinimaki, *supra* note 14).

found that 12.8% experienced hemorrhaging, 7.0% had incomplete abortions, and 11.0% needed surgical evacuation of "retained products of conception."[130] Because these statistics were similar to those of the adult cohort, the FDA found these statistics "reassuring" to support the safety profile of chemical abortion drugs for a pediatric population.[131]

215. The third and final study that the FDA cited in support of its PREA conclusion was a study of 28 adolescents, ages 14 to 17 years old, with pregnancies under 57 days' gestation.[132] Even though the authors of this study cautioned that a larger study was needed to make any generalizable conclusions for pediatric populations, the FDA likewise found this small study "reassuring."[133]

216. The FDA did not require any studies on the long-term effects of chemical abortion drugs in pediatric populations with developing reproductive systems.

XI. 2019 Citizen Petition

217. In response to the 2016 Major Changes, on March 29, 2019, Plaintiffs AAPLOG and American College of Pediatricians (2019 Petitioners) submitted to the FDA a citizen petition (2019 Citizen Petition) pursuant to 21 C.F.R. §§ 10.30 and 10.35; 21 C.F.R. Part 314, Subpart H (§§ 314.500–314.560); and Section 505 of the FFDCA (21 U.S.C. § 355). The 2019 Petitioners asked the FDA to (1) "restore and

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[130] Ex. 18, Niinimaki, *supra* note 14 at 3–4.
[131] Ex. 32, 2016 Summary Review at 20.
[132] *Id.* at 19.
[133] *Id.* at 20.

strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000" and, in the event that the FDA denied that request, (2) "retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS), and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescribers."[134]

218. The 2019 Citizen Petition asked the FDA to take the following actions to restore and strengthen elements of the chemical abortion drug regimen and prescriber requirements approved in 2000 to protect the health, safety, and welfare of women and girls:

- Reduce the maximum gestational age from 70 days to 49 days;
- Limit the ability to prescribe and dispense chemical abortion drugs to qualified, licensed physicians—not other "healthcare providers";
- Mandate certified abortionists to be physically present when dispensing chemical abortion drugs;
- Require that the prescriber perform an ultrasound to assess gestational age, identify ectopic pregnancies, ensure compliance with FDA restrictions, and adequately inform the woman of gestational age-specific risks, which rise with increasing gestational age;
- Restore the requirement for in-person administration of misoprostol;

[134] Ex. 35, 2019 Citizen Petition of AAPLOG to FDA (Mar. 29, 2019).

- Restore the requirement for an in-person follow-up visit to confirm abortion and rule out life-threatening infection through clinical examination or ultrasonographic scan;
- Restore the 2000 label language that stated that chemical abortion drugs are contraindicated if a woman lacks adequate access to emergency medical care; and
- Restore the prescriber reporting requirements for all serious adverse events, including any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the chemical abortion regimen.[135]

219. The 2019 Petitioners also asked the FDA to require a formal study of outcomes for at-risk populations, including the pediatric female population, patients with repeat chemical abortions, patients who have limited access to emergency room services, and patients who self-administer misoprostol.[136]

220. The 2019 Citizen Petition explained that "[t]he developmental stage of puberty involves a complex interplay of both progesterone and estrogen effects on the developing female reproductive system." Therefore, "[t]he use, and especially the potential multiple use, of Mifeprex, which is a powerful progesterone blocker, is

[135] *Id.*

[136] *Id.* at 13–14.

likely to significantly impact the developing reproductive system of the adolescent female."[137]

221. If the FDA refused to restore and strengthen the chemical abortion regimen and prescriber requirements approved in 2000, the 2019 Citizen Petition requested that the FDA retain the mifepristone REMS and continue limiting the dispensing of mifepristone to clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. In other words, the FDA should do no further harm to the few remaining safeguards for women and girls who undergo the chemical abortion drug regimen.[138]

222. In particular, the 2019 Petitioners explained that eliminating or relaxing the REMS to facilitate internet or telephone prescriptions would be dangerous to women and girls.[139] The 2019 Citizen Petition also raised concerns about dispensing from a pharmacy instead of a clinical facility.[140]

223. The 2019 Citizen Petition provided the FDA with detailed analysis and data to support these requests.

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[137] *Id.*
[138] *Id.* at 14–25.
[139] *Id.* at 18–20.
[140] *Id.* at 20–23.

XII. The FDA's Approval of a Generic Version of Mifeprex and a Single, Shared System REMS

224. On April 11, 2019, the FDA approved GenBioPro, Inc.'s[141] generic version of Mifeprex, "Mifepristone Tablets, 200 mg" (2019 ANDA Approval). The FDA determined GenBioPro's Mifepristone Tablets, 200 mg, "to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Mifeprex Tablets, 200 mg, of Danco Laboratories, LLC." GenBioPro's generic version of mifepristone has the same labeling and REMS as does Danco's Mifeprex.[142]

225. On the same day, the FDA approved modifications to the existing REMS for chemical abortion drugs to establish a single, shared system REMS for mifepristone products for the "medical termination of intrauterine pregnancy," thus allowing the FDA to have a uniform REMS for the chemical abortion drugs that two companies were now marketing. The FDA did not make any substantive modifications to the REMS approved in 2016.[143]

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[141] GenBioPro, Inc. is located at 3651 Lindell Road, Suite D1041, Las Vegas, Nevada. https://www.dnb.com/business-directory/company-profiles.genbiopro_inc.f925af03300887aacd053afe151fefb2.html.

[142] Ex. 36, 2019 FDA ANDA Approval Letter to GenBioPro, Inc. (Apr. 11, 2019), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/091178Orig1s000ltr.pdf.

[143] Ex. 37, 2019 FDA Supplemental Approval Letter to Danco Laboratories, LLC (Apr. 11, 2019), Supplement Approval, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/020687Orig1s022ltr.pdf.

XIII. 2020 ACOG-SMFM Letter to the FDA

226. On April 20, 2020, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) sent a joint letter (2020 ACOG-SMFM Letter), rather than a citizen petition, to the FDA asking the agency to remove in-person dispensing requirement for mifepristone during the COVID-19 pandemic and instead allow dispensing by mail or mail-order pharmacy.[144]

227. Following the letter, in May 2020, ACOG and others filed suit to enjoin the FDA's in-person dispensing requirement for mifepristone during the pandemic. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183 (D. Md. 2020).

228. The district court granted a nationwide preliminary injunction and lifted the in-person dispensing requirement for the pandemic. *Id.* at 233, order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020). The Fourth Circuit refused to stay the injunction. Court Order Denying Motion for Stay Pending Appeal, *Am. Coll. of Obstetricians & Gynecologists v. FDA,* Nos. 20-1824 (4th Cir. Aug. 13, 2020), ECF No. 30.

229. The FDA then filed for an emergency stay of the injunction with the U.S. Supreme Court. On January 12, 2021, the U.S. Supreme Court granted the FDA an emergency stay of the district court's injunction.[145]

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[144] Ex. 38, 2020 Letter from ACOG and SMFM, to FDA about Mifepristone REMS (Apr. 20, 2020) (2020 ACOG-SMFM Letter).

[145] *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (2021).

XIV. 2021 FDA Letter in Response to 2020 ACOG-SMFM Letter

230. President Joe Biden took office just eight days later. Acting under new management, the FDA responded to the 2020 ACOG-SMFM letter on April 12, 2021, and stated that the agency "intends to exercise enforcement discretion" during the COVID pandemic with respect to the in-person dispensing requirement of the REMS for mifepristone (2021 Non-Enforcement Decision).[146]

231. The FDA's 2021 Non-Enforcement Decision relied, in part, on the supposed lack of reported adverse events caused by chemical abortion drugs occurring between January 2020 and January 2021—despite the agency's elimination of non-fatal reporting requirements for abortionists in 2016. Nevertheless, in 2021, the FDA still "found that the small number of adverse events reported to FDA during the COVID-19 public health emergency (PHE) provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to the reported adverse events."[147]

232. The FDA's 2021 Non-Enforcement Decision neither acknowledged nor addressed the federal laws expressly prohibiting the distribution of mifepristone by mail, express company, or common carrier—despite explicitly recognizing that this action would allow "dispensing of mifepristone through the mail . . . or through a mail-order pharmacy."[148]

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[146] Ex. 39, 2021 FDA Letter to ACOG and SMFM About Mifepristone REMS, at 2 (Apr. 12, 2021) (2021 Non-Enforcement Decision).

[147] *Id.*

[148] *Id.*

XV. 2021 "Minor" Changes

233. On May 14, 2021, the FDA approved "minor" changes to the Patient Agreement Form to use "gender neutral language," replacing the pronouns "she" and "her" with "the patient." The FDA made similar revisions to the REMS document to reflect the removal of the gender-specific pronouns in the Patient Agreement Form.[149]

234. Despite these changes, the FDA did not require Danco to submit studies showing the safety and effectiveness of chemical abortion on women and girls who may be taking puberty blockers, testosterone injections, or other hormones in addition to the chemical abortion drugs.

235. Currently, the May 14, 2021, "minor" changes are the last updates to the REMS for chemical abortion drugs that the FDA has approved.[150] As discussed below, the FDA is requiring additional changes to the REMS.

XVI. The FDA's December 2021 Announcement of Further Reductions in Safeguards

236. On December 16, 2021, Defendant Cavazonni, Director of the FDA's Center for Drug Evaluation and Research, wrote a letter to Graham Chelius, M.D., of the Society of Family Planning and the California Academy of Family Physicians

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[149] Ex. 40, FDA Supplemental Approval Letter to Danco Laboratories, LLC (May 14, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/020687Orig1s024ltr.pdf.

[150] Ex. 41, 2021 Updated REMS for Mifepristone Tablets, 200mg (May 14, 2021), https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.

to inform him that the FDA had completed its review of the REMS for mifepristone.[151]

237. Although the FDA "determined that the Mifepristone REMS Program continues to be necessary to ensure that the benefits of the drug outweigh the risks," the agency "determined that it must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks."[152]

238. The letter identified specific new modifications to the REMS: "(1) removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the 'in-person dispensing requirement'); and (2) adding a requirement that pharmacies that dispense the drug be specially certified," signaling that the FDA will soon allow pharmacies to dispense chemical abortion drugs.[153]

239. Defendant Cavazzoni also noted that the FDA had answered the "related" 2019 Citizen Petition and would post the agency's response in the public docket.[154]

XVII. The FDA's Denial and Granting of the 2019 Citizen Petition

240. Accordingly, on December 16, 2021—the *same day* that Defendant Cavazzoni sent the letter to Dr. Chelius and *over 2.5 years* after receiving the 2019

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[151] Ex. 42, 2021 FDA Center for Drug Evaluation & Research Director Patrizia Cavazzoni Letter to Dr. Graham Chelius (Dec. 16, 2021).

[152] *Id.*

[153] *Id.*

[154] *Id.*

Citizen Petition—the FDA denied in part and granted in part the 2019 Citizen Petition (2021 FDA Response).[155]

241. The FDA granted the 2019 Citizen Petition only to the extent that the agency agreed that a REMS is necessary to ensure that the "benefits" of mifepristone in a regimen with misoprostol outweigh the risks. But the FDA retained only the Prescriber Agreement Form and the Patient Agreement Form as the remaining elements of the REMS.[156]

242. Aside from retaining these two remaining requirements, the FDA denied the 2019 Citizen Petition's requests (1) to restore and strengthen the mifepristone and prescriber requirements approved in 2000 and (2) to continue limiting the dispensing of mifepristone to women in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.[157]

243. Before addressing the merits of the 2019 Citizen Petition, the FDA discussed how chemical abortion drugs came to be regulated, starting with the 2000 Approval under Subpart H and the associated restrictions "needed to assure the safe use of the drug product." The FDA noted that it restricted the distribution of chemical abortion drugs under Subpart H, 21 C.F.R. § 314.520. The agency also

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[155] Ex. 43, 2021 FDA Letter to AAPLOG and Am. Coll. of Pediatricians denying in part and granting in part 2016 Citizen Petition, Docket No. FDA-2019-P-1534 (Dec. 16, 2021) (2021 FDA Response).

[156] *Id.* at 21–23.

[157] Ex. 43, 2021 FDA Response.

explained how and why chemical abortion drugs have an associated REMS to "assure safe use" due to the drug's approval under Subpart H.[158]

244. After providing this regulatory background, the FDA defended its decision in the 2016 Major Changes to reconsider and revise the safeguards codified in the original 2000 Approval and the subsequent REMS. The agency also disregarded the analyses and data set forth in the 2019 Citizen Petition.

245. The FDA repeated its previous justifications not to require studies in the pertinent pediatric population in the underlying 2000 Approval and the 2016 Major Changes, and it again asserted—without evidence—that "the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents."[159]

246. In response to the 2019 Citizen Petition's request to preserve the few safeguards after the 2016 Major Changes, the FDA stated that the REMS for mifepristone "must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks."[160]

247. In support of its claim that in-person dispensing is unnecessary, the FDA relied on the "small" number of adverse events voluntarily reported in the FDA Adverse Event Reporting System (FAERS) database to justify the elimination

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[158] *Id.* at 2–3.
[159] *Id.* at 38.
[160] *Id.* at 25

of this safeguard, even though the FDA had years ago removed the requirement for abortionists to report nonfatal adverse events.[161]

248. The FDA relied on the FAERS database despite conceding these facts: "FAERS data does have limitations"; the "FDA does not receive reports for every adverse event"; and thus "FAERS data cannot be used to calculate the incidence of an adverse event . . . in the U.S."[162]

249. The FDA likewise admitted that FAERS "is woefully inadequate to determine the post-marketing safety of mifepristone due to its inability to adequately assess the frequency or severity of adverse events" and the adverse events reported to the FDA "represent a fraction of the actual adverse events occurring in American women."[163] The FDA also agreed that there are reporting "discrepancies [that] render the FAERS inadequate to evaluate the safety of mifepristone abortions."[164]

250. The complicated FAERS electronic submission process further hinders the reporting of adverse events and exacerbates the unreliability of the number of

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[161] *Id.* at 25–36.

[162] Ex. 44, Questions and Answers on FDA's Adverse Event Reporting System (FAERS), https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers.

[163] Ex. 45, Kathi A. Aultman et al., *Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019*, 26 Law & Medicine 3, 25–26 (2021).

[164] Ex. 46, Christiana A. Cirucci et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act*, 8 Health Servs. Rsch & managerial Epidemiology 1 (2021).

adverse event reports. Doctors or other interested individuals seeking to submit an adverse event report must navigate a confusing webpage.[165] Recognizing this difficulty in submitting adverse event reports, the FDA provides a 48-page manual as guidance on the technical specifications for submitting an adverse event form.[166]

251. The FDA also relied on some published studies in making its 2021 decision to deny the 2019 Citizen Petition. The agency, however, noted that "the ability to generalize the results of these studies to the United States population is hampered," "the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy," and the FDA "did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States."[167]

252. Despite these limitations, the FDA concluded that mifepristone would "remain safe and efficacy [would] be maintained" if it removed the in-person dispensing requirement from the REMS program.[168]

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[165] Ex. 47, FDA, *FDA Adverse Event Reporting System (FAERS) Electronic Submissions*, https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions.

[166] Ex. 48, *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (April 2021), https://www.fda.gov/media/132096/download.

[167] Ex. 43, 2021 FDA Response at 28.

[168] *Id.*

253. The FDA's 2021 Petition Response neither acknowledged nor addressed the federal laws expressly prohibiting the distribution of mifepristone by mail, express company, or common carrier.

254. In summary, the following chart illustrates the changes to the mifepristone regimen over the years:

Regulation	**2000 Approval**	**2016 Major Changes**	**2021 Non-Enforcement Decision and Petition Denial**
Maximum Gestational Age	49 days	70 days	70 days
Dosage	• 600 mg of mifepristone • 400 mcg of misoprostol	• 200 mg of mifepristone • 800 mcg of misoprostol	• 200 mg of mifepristone • 800 mcg of misoprostol
Route of misoprostol administration	Vaginal	Buccal	Buccal
Timing of misoprostol administration	48 hours after mifepristone	24-48 hours after mifepristone	24-48 hours after mifepristone
Repeat dose of 800 mcg misoprostol	No	Yes	Yes
Dispensed only by or under the supervision of a physician	Yes	No	No
In-person *administration* of drug regimen	Yes	No	No
In-person *dispensing* of drug regimen	Yes	Yes	No
Follow-up in-person evaluation post-abortion	Yes	No	No
Requiring prescribers to report all non-fatal serious adverse events	Yes	No	No

XVIII. Injuries to Plaintiffs and Their Patients

255. The Alliance for Hippocratic Medicine, the AAPLOG, the American College of Pediatricians, and the Christian Medical & Dental Associations have members in Texas and around the country who have treated and will continue to treat women and girls who have suffered complications from the FDA's unlawful approval of chemical abortion drugs and subsequent elimination of the safeguards necessary to protect women and girls.

256. These medical associations sue on their own behalf and on behalf of their members and their members' patients—all of whom have been harmed and will continue to be harmed by the FDA's actions.

257. Dr. Jester practices medicine in Texas and has treated a woman who suffered complications from the FDA's unlawful approval of chemical abortion drugs and elimination of the safeguards necessary to protect women and girls. Dr. Frost-Clark, Dr. Johnson, and Dr. Delgado have also treated women and girls who have suffered complications from the FDA's unlawful approval of chemical abortion drugs and elimination of the safeguards necessary to protect women and girls.

258. These doctors sue on behalf of themselves and their patients—both of whom have been harmed and will continue to be harmed by the FDA's actions.[169]

[169] *June Med. Servs. LLC v. Russo*, 140 S. Ct. 2103, 2118–20 (2020) (holding that doctors and medical providers had third-party standing on behalf of their patients because the Court has "long permitted" them "to invoke the rights of their actual or potential patients").

259. The sworn declarations attached to the Complaint detail how each Plaintiff has been, is, and/or will be personally and professionally injured by the FDA's actions. As many of their injuries overlap, the injuries discussed below cite the specific Plaintiff declaration(s) associated with those injuries. The Complaint incorporates by reference each of the allegations in these declarations.

A. Injuries to Patients

260. The FDA's 2000 Approval legalized an unsafe drug regimen.[170]

261. Chemical abortion drugs cause women and girls to suffer many intense side effects, including cramping, heavy bleeding, and severe pain.[171]

262. Women and girls who take chemical abortion drugs experience significantly more complications than those who have surgical abortions.[172]

263. The FDA's 2000 Approval has caused women and girls to suffer complications from chemical abortion.[173]

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[170] *See* Compl. ¶¶ 141–158.

[171] Ex. 4, Harrison Decl. ¶ 23; Ex. 9, Wozniak Decl. ¶ 17; Ex. 8, Skop Decl. ¶ 13; Ex. 49, Johnson Decl. ¶ 8; Ex. 50, Frost-Clark Decl. ¶ 9; Ex. 51, Delgado Decl. ¶ 11.

[172] Ex. 4, Harrison Decl. ¶ 22; Ex. 9, Wozniak Decl. ¶ 15; Ex. 8, Skop Decl. ¶ 19; Ex. 10, Foley Decl. ¶ 8; Ex. 51, Delgado Decl. ¶ 11.

[173] Ex. 4, Harrison Decl. ¶ 24; Ex. 7, Francis Decl. ¶ 10; Ex. 9, Wozniak Decl. ¶ 8; Ex. 8, Skop Decl. ¶¶11–13, 16–19, 22–23; Ex. 52, Jester Decl. ¶ 16; Ex. 49, Johnson Decl. ¶¶ 9–11; Ex. 10, Foley Decl. ¶ 3; Ex. 50, Frost-Clark Decl. ¶ 7; Ex. 3, Dickerson Decl. ¶ 11.

264. Since the 2016 Major Changes, the rate of women and girls who have suffered complications from chemical abortion and required critical medical treatment has increased and will continue to increase.[174]

265. The FDA's decision to expand the gestational age for approved mifepristone use to 70 days (10 weeks) harms women.[175]

266. This expansion of the permissible gestational age is especially dangerous for women and girls when combined with the FDA's elimination of the in-person dispensing and follow-up visit requirements.[176]

267. The FDA's failure to require an ultrasound, its subsequent elimination of in-person drug administration, physician supervision, and patient follow-up, and, finally, its removal of the requirement of in-person dispensing in specified health care settings, exposes women and girls to increased risk of suffering complications from chemical abortion and requiring further medical attention following the drug regimen.[177]

268. Because the FDA does not require it, many abortionists do not remain physically near women and girls during the most painful and excruciating periods of

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[174] Ex. 4, Harrison Decl. ¶ 26; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶ 18; Ex. 52, Jester Decl. ¶ 23; Ex. 49, Johnson Decl. ¶ 9; Ex. 10, Foley Decl. ¶ 10; Ex. 51, Delgado Decl. ¶¶ 16, 18; Ex. 3, Dickerson Decl. ¶ 11.

[175] Ex. 9, Wozniak Decl. ¶ 10; Ex. 52, Jester Decl. ¶ 17.

[176] Ex. 52, Jester Decl. ¶ 13.

[177] Ex. 4, Harrison Decl. ¶¶ 24–31; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶¶ 8–10, 14; Ex. 8, Skop Decl. ¶¶ 20, 25–29; Ex. 5, Barrows Decl. ¶¶ 15–18; Ex. 52, Jester Decl. ¶¶ 15–18, 22–23, 25; Ex. 10, Foley Decl. ¶ 9; Ex. 50, Frost-Clark Decl. ¶¶ 12–15.

the chemical abortion drug regimen, often sending them home with the drugs. Given their lack of admitting privileges and treatment capabilities, abortionists usually instruct women to go to the emergency department of the closest hospital for treatment of any severe adverse events.[178]

269. The FDA has eliminated all procedural safeguards that would rule out ectopic pregnancies, verify gestational age, identify any contraindications to prescribing mifepristone, or identify potential complications like sepsis and hemorrhage, remaining fetal parts, and others until the patient is at a critical time or it is too late to help the patient. As a result, women and girls often suffer unexpected episodes of heavy bleeding or severe pain and must rush to the emergency department of the nearest hospital.[179]

270. As more women and girls require treatment in emergency departments, the other patients of the treating doctors are adversely affected. With the increase in women and girls suffering emergency complications from chemical abortion or seeking to reverse the effects of the chemical abortion regimen, there is a direct correlation in the decrease in time, attention, and resources that emergency department doctors have to treat their other patients.[180]

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[178] Ex. 4, Harrison Decl. ¶ 19; Ex. 10, Foley Decl. ¶ 11.

[179] Ex. 8, Skop Decl. ¶¶ 13, 17–18, 22–23, 28–29; Ex. 5, Barrows Decl. ¶¶ 17–18; Ex. 52, Jester Decl. ¶¶ 13, 15–16, 23; Ex. 10, Foley Decl. ¶ 9; Ex. 50, Frost-Clark Decl. ¶¶ 12–15.

[180] Ex. 9, Wozniak Decl. ¶¶ 17–18, 27; Ex. 7, Francis Decl. ¶ 12; Ex. 49, Johnson Decl. ¶¶ 14, 16; Ex. 8, Skop Decl. ¶ 32; Ex. 10, Foley Decl. ¶ 10; Ex. 51, Delgado Decl. ¶ 18; Ex. 3, Dickerson Decl. ¶ 14.

271. Abortionists commonly violate the remaining safeguards and the FDA-approved label for chemical abortion drugs by giving the drugs to women who are contraindicated for chemical abortion (i.e., could experience deadly adverse events if they take the drugs) and then subsequently harmed by these drugs, demonstrating that the FDA's remaining safeguards for women and girls are ineffective in protecting them.[181]

272. The FDA's decision not to require abortionists to report all adverse events for chemical abortion drugs harms women and girls because it creates an inaccurate and false safety profile for the use of chemical abortion drugs.[182]

273. Due to inadequate adverse event reporting, the true rates of risks associated with chemical abortion drugs remain undercounted and therefore are unknown. Because abortion providers cannot know the accurate risk levels that their patients face when ingesting these drugs, these providers cannot properly inform their patients about the risks associated with chemical abortion. This prevents women and girls from giving informed consent to these providers.[183]

274. Many women and girls do not fully understand the nature of chemical abortion drugs and the risks that these drugs present to them.[184]

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[181] Ex. 9, Wozniak Decl. ¶ 24.

[182] Ex. 4, Harrison Decl. ¶ 35; Ex. 52, Jester Decl. ¶ 24.

[183] Ex. 4, Harrison Decl. ¶¶ 36–38; Ex. 9, Wozniak Decl. ¶¶ 19–20; Ex. 49, Johnson Decl. ¶ 17.

[184] Ex. 4, Harrison Decl. ¶ 31; Ex. 8, Skop Decl. ¶¶ 13, 27; Ex. 52, Jester Decl. ¶ 24; Ex. 49, Johnson Decl. ¶ 12; Ex. 10, Foley Decl. ¶¶ 12, 15; Ex. 51, Delgado Decl. ¶ 15.

275. Abortionists who prescribe or dispense chemical abortion drugs are not providing women with an adequate, accurate assessment of the known risks and effects associated with chemical abortion. Therefore, women and girls are unable to give informed consent to the drugs they are receiving, and thus they are not consenting at all to taking the chemical abortion drugs—resulting in physical and mental injuries.[185]

276. Women and girls often suffer distress and regret after undergoing chemical abortion, sometimes seeking to reverse the effects of mifepristone.[186]

277. A woman or girl can experience these emotions and feelings upon viewing the body of her lifeless baby after taking chemical abortion drugs.[187]

278. Even with medical oversight, abortionists can sometimes coerce women into taking chemical abortion drugs—without their true informed consent.[188]

279. The FDA's actions to eliminate in-person dispensing and administration also harm women because the lack of oversight will likely exacerbate human trafficking. Many trafficked women experience abortions and doctors potentially serve as an important resource to intervene on behalf of these trafficked women and girls.[189]

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[185] Ex. 4, Harrison Decl. ¶ 37; Ex. 8, Skop Decl. ¶¶ 14, 16, 27; Ex. 49, Johnson Decl. ¶ 12; Ex. 10, Foley Decl. ¶ 15; Ex. 50, Frost-Clark Decl. ¶ 20; Ex. 51, Delgado Decl. ¶ 15.

[186] Ex. 8, Skop Decl. ¶¶ 15–16; Ex. 10, Foley Decl. ¶¶ 12, 16; Ex. 51, Delgado Decl. ¶ 14.

[187] Ex. 8, Skop Decl. ¶ 15.

[188] Ex. 51, Delgado Decl. ¶ 15.

[189] Ex. 8, Skop Decl. ¶ 31.

280. Women and girls will continue to suffer complications from chemical abortion drugs.[190]

B. Injuries to Plaintiff Doctors

281. Because the FDA's 2000 Approval of chemical abortion drugs legalized an unsafe drug regimen, women and girls have suffered many intense side effects and increasing complications—requiring crucial medical attention and treatment.[191]

282. The FDA's 2000 Approval has caused medical professionals, including Plaintiff doctors and the members of Plaintiff medical associations, to treat women and girls who have suffered complications from mifepristone and misoprostol.[192]

283. Since the 2016 Major Changes and the associated elimination of necessary safeguards for women and girls, medical professionals, including Plaintiff doctors and the members of Plaintiff medical associations, have seen and will continue to see an additional increase in the rate of women and girls who have suffered complications from chemical abortion—complications requiring critical treatment from these doctors.[193]

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[190] Ex. 4, Harrison Decl. ¶ 26; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶ 29; Ex. 8, Skop Decl. ¶ 21; Ex. 52, Jester Decl. ¶ 20; Ex. 49, Johnson Decl. ¶ 18.

[191] Ex. 4, Harrison Decl. ¶ 23; Ex. 9, Wozniak Decl. ¶¶ 15, 17; Ex. 8, Skop Decl. ¶¶ 13, 18; 23; Ex. 5, Barrows Decl. ¶ 17; Ex. 49, Johnson Decl. ¶ 8; Ex. 50, Frost-Clark Decl. ¶ 9; Ex. 51, Delgado Decl. ¶ 11; Ex. 10, Foley Decl. ¶ 8; Ex. 3, Dickerson Decl. ¶ 11.

[192] Ex. 4, Harrison Decl. ¶ 24; Ex. 7, Francis Decl. ¶ 10; Ex. 8, Skop Decl. ¶¶ 12–21; Ex. 52, Jester Decl. ¶ 17; Ex. 49, Johnson Decl. ¶ 9; Ex. 10, Foley Decl. ¶ 3; Ex. 50, Frost-Clark Decl. ¶ 7; Ex. 3, Dickerson Decl. ¶¶ 11, 13.

[193] Ex. 4, Harrison Decl. ¶ 26; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶ 18; Ex. 52, Jester Decl. ¶¶ 18, 23, 25; Ex. 49, Johnson Decl. ¶ 9; Ex. 10, Foley Decl. ¶ 9; Ex. 50, Frost-Clark Decl. ¶¶ 12–15; Ex. 51, Delgado Decl. ¶¶ 13, 16; Ex. 3, Dickerson Decl. ¶ 12.

284. The FDA's approved regimen for chemical abortion drugs harms not only women and girls but also medical professionals, including Plaintiff doctors and the members of Plaintiff medical associations, who respond and treat these complications and other effects from chemical abortion drugs.[194]

285. The FDA's elimination of most of the safeguards protecting women and girls from the dangers of mifepristone has made chemical abortion more widely available and with less medical supervision—causing more women and girls to experience complications from chemical abortion and, therefore, increasing emergency situations. An increase in complications only compounds the harm to doctors, including Plaintiff doctors and the members of Plaintiff medical associations.[195]

286. When women and girls suffer complications from chemical abortion drugs, these adverse events can overwhelm the medical system and consume crucial limited medical resources, including blood for transfusions, physician time and attention, space in hospitals and medical centers, and other equipment and

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[194] Ex. 4, Harrison Decl. ¶¶ 26–30; Ex. 7, Francis Decl. ¶¶ 12–13; Ex. 9, Wozniak Decl. ¶ 17; Ex. 8, Skop Decl. ¶¶ 25, 32; Ex. 52, Jester Decl. ¶¶ 17, 18; Ex. 49, Johnson Decl. ¶ 14; Ex. 51, Delgado Decl. ¶ 13; Ex. 3, Dickerson Decl. ¶ 12.

[195] Ex. 52, Jester Decl. ¶¶ 20, 25; Ex. 50, Frost-Clark Decl. ¶ 8; Ex. 4, Harrison Decl. ¶¶ 26–30, 28; Ex. 7, Francis Decl. ¶ 14; Ex. 8, Skop Decl. ¶¶ 20, 28, 32; Ex. 49, Johnson Decl. ¶ 14; Ex. 10, Foley Decl. ¶ 10.

medicines.[196] This need for blood transfusions exacerbates the current critical national blood shortage.[197]

287. The increased occurrence of complications related to chemical abortion drugs multiplies the workload of health care providers, including Plaintiff doctors and the members of Plaintiff medical associations, in some cases by astronomical amounts. This is especially true in maternity care "deserts" (i.e., geographic areas where there are not a large number of OB/Gyn providers for patients).[198]

288. When there is a complication from chemical abortion drugs, the typical care doctors provide patients moves from simple patient management to complicated patient management. Accordingly, a patient who suffers complications from chemical abortion drugs requires significantly more time and attention from providers than most patients require.[199]

289. For example, Plaintiff Dr. Jester needed to treat a woman who had traveled from Texas to New Mexico to obtain chemical abortion drugs from Planned Parenthood. The woman returned to Texas, suffered from two weeks of moderate to heavy bleeding, and then developed a uterine infection. At the hospital, Dr. Jester provided her with intravenous antibiotics and performed a dilation and curettage

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[196] Ex. 4, Harrison Decl. ¶ 28; Ex. 7, Francis Decl. ¶ 17; Ex. 9, Wozniak Decl. ¶ 17.

[197] Ex. 4, Harrison Decl. ¶ 19; *see also* Current National Blood Supply, https://americasblood.org/for-donors/americas-blood-supply/ (last visited Nov. 16, 2022); Catherine Garcia, *The urgent American blood shortage, explained*, The Week (Oct. 26, 2022), https://theweek.com/health-and-wellness/1017643/the-urgent-american-blood-shortage-explained.

[198] Ex. 4, Harrison Decl. ¶ 29; Ex. 7, Francis Decl. ¶ 14; Ex. 9, Wozniak ¶¶ 17–18.

[199] Ex. 4, Harrison Decl. ¶ 30.

(i.e., the surgical procedure to remove a dead baby and pregnancy tissue from inside the uterus). If she had waited a few more days before receiving care from Dr. Jester, she could have been septic and died.[200]

290. Dr. Nancy Wozniak, a member of Plaintiff AAPLOG, needed to treat a woman who had contraindications to chemical abortion drugs (due to her taking anti-coagulants) but still received chemical abortion drugs from Planned Parenthood in Indiana. The woman consumed the first chemical abortion drug, mifepristone, at Planned Parenthood and took an Uber for a ride home. During her Uber ride, she began to experience bleeding and other adverse side effects from the mifepristone. Instead of taking her home, the Uber driver took her to the emergency department of Dr. Wozniak's hospital. Dr. Wozniak treated the woman and advised her not to take the second chemical abortion drug, misoprostol, because of the grave risk that she could bleed out and die.[201]

291. The FDA's elimination of the in-person dispensing requirement for chemical abortion drugs—allowing mail-order abortion—further harms the practice of medicine. The increasing number of chemical abortions through mail-order or telemedicine methods means that more women and girls will suffer complications and require medical attention from doctors, including Plaintiff doctors and the

[200] Ex. 52, Jester Decl. ¶ 17.

[201] Ex. 9, Wozniak Decl. ¶¶ 24–25.

members of Plaintiff medical associations, especially given that remote abortionists often cannot or do not treat such complications.[202]

292. To circumvent state laws that regulate abortions and protect the health and safety of women and girls, abortionists are relying on access to chemical abortion drugs through mail-order schemes or telemedicine, further increasing the use of these drugs and the complications associated with them.[203]

293. As more emergency situations arise, emergency room doctors, such as Plaintiff doctors and the members of Plaintiff medical associations, are having to treat more patients, including performing hysterectomies or removing fetal parts remains. The more patients suffering emergency complications from chemical abortion or seeking to reverse the chemical abortion process, the less time and attention these doctors have to treat their other patients.[204]

294. Because abortionists do not adequately describe what happens during a chemical abortion and give these drugs to women and girls to take outside of the abortion facility, doctors have needed to treat and care for many women who have come to the emergency department for their intense bleeding and other effects of

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[202] Ex. 9, Wozniak Decl. ¶ 14; Ex. 5, Barrows Decl. ¶ 17; Ex. 52, Jester Decl. ¶¶ 22–23; Ex. 50, Frost-Clark Decl. ¶ 12–15; Ex. 10, Foley Decl. ¶ 10.

[203] Ex. 9, Wozniak Decl. ¶ 13; Ex. 10, Foley Decl. ¶ 10; *see also* Ruth Reader, *State abortion bans prove easy to evade*, Politico (Nov. 11, 2022, 2:24 PM), https://www.politico.com/news/2022/11/01/state-abortion-bans-medication-00064407; Emily Bazelon, *Risking Everything to Offer Abortions Across State Lines*, New York Times (Oct. 4, 2022), https://www.nytimes.com/2022/10/04/magazine/abortion-interstate-travel-post-roe.html.

[204] Ex. 9, Wozniak Decl. ¶¶ 17–18, 27; Ex. 7, Francis Decl. ¶ 14; Ex. 49, Johnson Decl. ¶¶ 14, 16; Ex. 8, Skop Decl. ¶ 32; Ex. 51, Delgado Decl. ¶ 18.

the chemical abortion drugs—although not considered complications from the regimen.[205]

295. Doctors, including Plaintiff doctors and the members of Plaintiff medical associations, experience enormous pressure, stress, and chaos in these emergency situations that the FDA created through its approval of chemical abortion drugs and elimination of necessary safeguards.[206]

296. Some of these emergency situations force pro-life doctors, including Plaintiff doctors and the members of Plaintiff medical associations, into situations in which they feel complicit in an elective chemical abortion by needing to remove a baby with a beating heart or pregnancy tissue as the only means to save the life of the woman or girl. This feeling of complicity in the act of an elective chemical abortion causes great emotional suffering, mental anguish, and spiritual distress among these doctors.[207]

297. For example, Dr. Ingrid Skop, a member of Plaintiff AAPLOG, needed to treat a young woman who had been bleeding for six weeks after she took chemical abortion drugs at a Planned Parenthood facility. After two follow-up appointments, Planned Parenthood had given her an additional dose of the second chemical abortion drug, misoprostol, which failed to resolve her complications. When Dr. Skop treated the young woman, Dr. Skop performed a sonogram,

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[205] Ex. 10, Foley Decl. ¶ 15; Ex. 49, Johnson Decl. ¶ 11.

[206] Ex. 9, Wozniak Decl. ¶ 17; Ex. 5, Barrows Decl. ¶ 19; Ex. 52, Jester ¶ 20; Ex. 49, Johnson ¶ 15; Ex. 3, Dickerson Decl. ¶ 14.

[207] Ex. 8, Skop Decl. ¶ 34; Ex. 7, Francis Decl. ¶ 13; Ex. 5, Barrows Decl. ¶ 26; Ex. 3, Dickerson Decl. ¶ 16.

identified a significant amount of pregnancy tissue remaining in the woman's uterus, and had to perform a suction aspiration to resolve her complication.[208]

298. The members of Plaintiff medical associations oppose being forced to end the life of a human being in the womb for no medical reason, including by having to complete an incomplete elective chemical abortion. The objections are both ethical and medical as they stem from the purpose of medicine itself, which is to heal and not to electively kill human beings regardless of their location. Accordingly, Plaintiff medical associations and their members are harmed by the FDA's repeated removal of necessary safeguards, which may force them to treat women and girls seeking the completion of an elective chemical abortion. This concern is real and imminent, especially in light of the Biden HHS's impermissible actions to compel doctors to complete elective chemical abortions under the Emergency Medical Treatment and Active Labor Act (EMTALA).[209]

299. The FDA's loosening of chemical abortion regulations impacts the standard of care for chemical abortion drugs and the demands and expectations that hospitals will put on their physicians.[210]

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[208] Ex. 8, Skop Decl. ¶ 23.

[209] Ex. 4, Harrison Decl. ¶ 44; Ex. 5, Barrows Decl. ¶ 26; Ex. 3, Dickerson Decl. ¶ 16; *see also Reinforcement of EMTALA Obligations specific to Patients who are Pregnant or are Experiencing Pregnancy Loss (QSO-21-22-Hospitals- UPDATED JULY 2022)*, https://www.cms.gov/files/document/qso-22-22-hospitals.pdf.

[210] Ex. 5, Barrows Decl. ¶ 25.

300. It grieves Plaintiff doctors and members of Plaintiff medical associations to treat women and girls harmed by chemical abortion drugs, including those who regret their decision to have a chemical abortion.[211]

301. When their patients have chemical abortions, doctors lose the opportunity to provide professional services and care for the woman and child through pregnancy, which causes harms to providers who no longer can care for their patients and bring about a successful delivery of a new life.[212]

302. The FDA's elimination of the requirement for abortionists to report all adverse events related to chemical abortion drugs leads to unreliable reporting. Without an accurate understanding of the adverse effects of widespread chemical abortion drug use, Plaintiff doctors and members of Plaintiff medical associations cannot effectively practice evidence-based medicine. Health care providers cannot assess the risks of a particular course of treatment if the FDA is not collecting and tracking the risks. And, therefore, they cannot accurately advise their patients and the public about these risks.[213]

303. Many doctors likely do not know about the importance of reporting adverse events related to chemical abortion drugs to the FDA. Similarly, many doctors likely do not know how to report adverse events.[214]

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[211] Ex. 52, Jester Decl. ¶ 27; Ex. 8, Skop Decl. ¶ 33; Ex. 51, Delgado ¶ 14.

[212] Ex. 51, Delgado Decl. ¶ 17; Ex. 52, Jester Decl. ¶ 19.

[213] Ex. 9, Wozniak Decl. ¶¶ 19–20; Ex. 5, Barrows Decl. ¶ 19; Ex. 8, Skop Decl. ¶ 30; Ex. 4, Harrison Decl. ¶¶ 36–39; Ex. 52, Jester Decl. ¶¶ 24, 26; Ex. 49, Johnson Decl. ¶ 17; Ex. 10, Foley Decl. ¶ 17; Ex. 50, Frost-Clark Decl. ¶ 22.

[214] Ex. 4, Harrison Decl. ¶ 33.

304. Even when Plaintiff doctors and members of Plaintiff medical associations want to voluntarily report adverse events associated with chemical abortion to the FDA, they must go through the complicated, cumbersome, and time-consuming FAERS submission process. The adverse event reporting requirements and the FAERS submission process harm medical practices by taking away significant time from a doctor to treat and meet with patients.[215]

305. In addition, even when doctors want to voluntarily report adverse events to the manufacturer, Danco, the doctor must print, fill out by hand, and then either mail or email back the form to Danco. Much of the information required by this form is impossible to obtain by the physician seeing the patient if they were not the one who dispensed the medication (such as lot number and dosage)—forcing the doctor to leave several fields blank. There is no confirmation whether the reported complications were recorded by Danco or reported to the FDA. Regardless, this submission process harms medical practices by taking away significant time from a doctor to treat and meet with patients.[216]

306. Even when doctors want to report adverse events to their state regulators, their reports can be rejected for improper reasons (e.g., asserting that there was no adverse event because the doctor saved and treated the woman injured by chemical abortion drugs).[217]

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[215] Ex. 7, Francis Decl. ¶¶ 16–18; Ex. 4, Harrison Decl. ¶ 33–34; Ex. 50, Frost-Clark Decl. ¶ 23.

[216] Ex. 7, Francis Decl. ¶¶ 16–18.

[217] Ex. 9, Wozniak Decl. ¶ 26.

307. Because many women and girls suffering complications from chemical abortion drugs tell emergency department doctors that they are experiencing miscarriages, these doctors might not report these incidences as adverse events and so these complications are significantly underreported or not fully known.[218]

308. The inability or refusal of a patient to disclose why she is presenting herself in the emergency department or what drugs she has received also impedes the ability of doctors, including Plaintiff doctors and the members of Plaintiff medical associations, to practice medicine and provide proper treatment to these patients.[219]

309. The lack of accurate information on adverse events also harms the doctor-patient relationship with all medical care providers because the patients no longer trust that their health care providers are telling them the truth. This harms even doctors who do not support or practice chemical abortions, such as the members of the AAPLOG.[220]

310. The FDA's removal of necessary safeguards for women and girls who use chemical abortion drugs increases physicians' exposure to potential liability. Emergency department physicians often have no prior relationship with the patient, lack access to the patient's medical history, and encounter patients who do not know what drugs they consumed or conceal the fact that they attempted a

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[218] Ex. 9, Wozniak Decl. ¶ 28; Ex. 10, Foley Decl. ¶ 14.

[219] Ex. 9, Wozniak Decl. ¶ 28; Ex. 49, Johnson Decl. ¶¶ 13, 15; Ex. 10, Foley Decl. ¶ 14; Ex. 50, Frost-Clark Decl. ¶¶ 16–17, 19.

[220] Ex. 4, Harrison Decl. ¶ 37.

chemical abortion. These factors place physicians in higher-risk situations with less critical information about patients, thus increasing their exposure to allegations of malpractice and potential liability.[221]

311. As this exposure increases, so does the cost to practice medicine, including insurance costs.[222]

312. Doctors, such as Dr. Jester and Dr. Delgado, serve patients as professional health care providers. They provide care to all women and unborn children, and they give them the best professional services possible. Just like all other health care providers, a hospital or practice will bill for the costs of medical services rendered. When their patients have chemical abortions, they lose the opportunity to provide professional medical care for the woman and child through pregnancy and bring about a successful delivery of a new life.[223]

313. Plaintiffs expect to continue to treat women and girls who suffer complications from chemical abortion drugs.[224]

C. Injuries to Plaintiff Medical Associations

314. Plaintiffs medical associations have also suffered organizational harms from the FDA's approval and deregulation of chemical abortion drugs.

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[221] Ex. 9, Wozniak Decl. ¶¶ 21–22; Ex. 5, Barrows Decl. ¶¶ 22–24; Ex. 52, Jester Decl. ¶ 21; Ex. 49, Johnson Decl. ¶ 15; Ex. 10, Foley Decl. ¶ 14; Ex. 50, Frost-Clark Decl. ¶¶ 16–18; Ex. 3, Dickerson Decl. ¶ 15.

[222] Ex. 5, Barrows Decl. ¶ 24.

[223] Ex. 52, Jester Decl. ¶ 19; Ex. 51, Delgado ¶ 17.

[224] Ex. 4, Harrison Decl. ¶ 26; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶ 29; Ex. 8, Skop Decl. ¶ 21; Ex. 52, Jester Decl. ¶¶ 12, 20; Ex. 49, Johnson Decl. ¶ 18.

315. For example, the inability to share accurate information with member physicians, their patients, and the public on the risks of chemical abortion frustrates and complicates Plaintiff medical associations' purpose to support women's health and to educate doctors, their patients, and the public about these dangers.[225]

316. In addition, Plaintiff AAPLOG has needed to divert limited time, energy, and resources to compensate for this lack of information by conducting their own studies and analyses of the available data. This diversion of time, energy, and resources comes to the detriment of other advocacy and educational efforts of Plaintiff AAPLOG, including their efforts about the dangers of surgical abortion, the conscience rights of doctors, and the sanctity of life at all stages.[226]

317. Plaintiffs AAPLOG and Christian Medical & Dental Associations submitted a citizen petition in 2002 challenging the FDA's 2000 Approval of chemical abortion drugs and requesting an audit of the clinical studies. Both associations were concerned about women's health issues and recognized that the FDA's violations of its standards and rules in approving chemical abortion drugs put the lives and health of women and girls at risk. It took considerable time, energy, and resources to draft their 92-page petition and the 30-page response to comments letter, in addition to compiling and analyzing supporting sources and

[225] Ex. 4, Harrison Decl. ¶¶ 38–39; Ex. 7, Francis Decl. ¶¶ 19–20; Ex. 5, Barrows Decl. ¶¶ 20–21; Ex. 6, Van Meter Decl. ¶¶ 19–20; Ex. 3, Dickerson Decl. ¶¶ 21–22.
[226] Ex. 4, Harrison Decl. ¶ 40; Ex. 7, Francis Decl. ¶ 21.

studies. This effort caused both associations to divert limited time, energy, and resources from its other priorities and routine functions.[227]

318. Similarly, Plaintiffs AAPLOG and American College of Pediatricians submitted another citizen petition in 2019 challenging the FDA's 2016 Major Changes to the chemical abortion drug regimen. It also took considerable time, energy, and resources to draft the 26-page petition, in addition to compiling and analyzing supporting sources and studies. This effort caused both associations to divert limited time, energy, and resources from its other priorities and routine functions.[228]

319. The Catholic Medical Association, a member of the Alliance for Hippocratic Medicine, has also taken actions to challenge the FDA's approval and deregulation of chemical abortion drugs—at the expense of other priorities.[229]

320. Because abortion activists continue to file their own citizen petitions and letters with the FDA asking the agency to eliminate all protections for women and girls who take chemical abortion drugs, and knowing the Biden administration's relentless, politicized efforts to push these drugs throughout the country, Plaintiff medical associations continue to expend considerable time, energy, and resources on its public advocacy and educational activities about chemical abortion drugs—to the detriment of their other priorities and functions.

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[227] Ex. 4, Harrison Decl. ¶ 41; Ex. 7, Francis Decl. ¶ 22; Ex. 5, Barrows Decl. ¶ 27.
[228] Ex. 4, Harrison Decl. ¶ 42; Ex. 7, Francis Decl. ¶ 23; Ex. 6, Van Meter Decl. ¶ 21.
[229] Ex. 3, Dickerson Decl. ¶¶ 17–20.

This diversion of time, energy, and resources will not cease until the FDA's approval and deregulation of chemical abortion drugs cease.[230]

XIX. The Need for Judicial Relief

321. Injunctive relief is necessary to prevent these harms, and judicial relief is appropriate to vacate, set aside, enjoin, and declare these acts unlawful.

322. All of the agency actions at issue—the 2000 Approval, the 2016 Petition Denial, the 2016 Major Changes, the 2019 ANDA Approval, the 2021 Non-Enforcement Decision, and the 2021 Petition Response, as well as the agency's failure to act and prohibit or restrict chemical abortion drugs—are final agency actions subject to judicial review under the APA.

323. All the acts of Defendants described above, and their officers, agents, employees, and servants, were executed and are continuing to be executed by Defendants under the color and pretense of the policies, statutes, ordinances, regulations, customs, and usages of the United States.

324. Under 5 U.S.C. § 701(a), no statute precludes judicial review of the agency's actions, and the actions are not committed to agency discretion by law.

325. Under the APA, a reviewing court must "hold unlawful and set aside agency action, findings, and conclusions" if they are "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right." 5 U.S.C. § 706(2)(C).

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[230] Ex. 4, Harrison Decl. ¶ 43; Ex. 7, Francis Decl. ¶ 24; Ex. 5, Barrows Decl. ¶ 27; Ex. 6, Van Meter Decl. ¶ 22; Ex. 3, Dickerson Decl. ¶ 20.

326. Under the APA, a reviewing court must "hold unlawful and set aside agency action, findings, and conclusions" if they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

327. Likewise, a court must "compel agency action unlawfully withheld." 5 U.S.C. § 706(1).

328. Plaintiffs have no adequate remedy available at law.

329. Plaintiffs have no adequate or available administrative remedy. In the alternative, any administrative remedy would be futile or unnecessary.

330. Defendants would suffer no harm from the relief requested, and the relief requested would serve the public interest.

CLAIMS FOR RELIEF

CLAIM ONE

2000 APPROVAL

ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706) IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT; ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

331. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

332. Defendants lacked legal authority in 2000 to approve mifepristone under the FDA's Subpart H regulations.

I. Subpart H

333. The FDA's Subpart H regulations apply only to "certain new drugs that have been studied for their safety and effectiveness in treating serious or life-

threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)." 21 C.F.R. § 314.500.

334. Pregnancy is not an illness.

335. Pregnancy is neither "serious" nor "life-threatening," as those terms are understood in Subpart H.

336. Chemical abortion does not provide a "meaningful therapeutic benefit to patients over existing treatments."

337. Defendants lacked the authority to approve mifepristone for chemical abortion under Subpart H in 2000.

338. Because the French and American trials did not compare the Mifeprex regimen with the then-existing method for ending pregnancies (i.e., surgical abortion), the trials did not demonstrate a "meaningful therapeutic benefit over existing therapy."

339. Thus, the FDA's 2000 Approval of mifepristone for chemical abortion was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with Subpart H's provision for the accelerated approval of certain new drugs.

II. FFDCA

340. Defendants lacked legal authority in 2000 to approve mifepristone under the FFDCA.

341. The FDA's 2000 Approval violated the FFDCA because the clinical trials on which the agency relied did not use the full set of design features the

agency typically requires to produce unbiased investigations of drug safety and effectiveness.

342. Because these trials were not blinded, randomized, or concurrently controlled, they did not establish the safety and effectiveness of the Mifeprex regimen.

343. The FDA also failed to perform a statistical analysis of the data from the U.S. Clinical Trial.

344. The FDA impermissibly extrapolated conclusions about the safety and effectiveness of mifepristone from the U.S. Clinical Trial even though the agency did not retain the requirements governing physician training, ultrasound, the post-misoprostol waiting period, or physician privileges at facilities that provide emergency care. The U.S. Clinical Trial failed to meet the requirements of the FFDCA that the trial demonstrates safety and effectiveness under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. Instead, the FDA had insufficient information on whether mifepristone was safe under such conditions.

345. Finally, the FDA violated the FFDCA and the agency's implementing regulations because the agency mandated the use of misoprostol for chemical abortion as part of the 2000 Approval—despite the requirement that the sponsor submit an sNDA for a new use of a previously approved drug.

346. Therefore, Defendants lacked the authority to approve mifepristone for chemical abortion under the FFDCA. Given these infirmities, the 2000 Approval

was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with the FFDCA.

III. PREA

347. Defendants lacked legal authority in 2000 to approve mifepristone under PREA.

348. In the 2000 Approval, the FDA stated that it was "waiving the pediatric study requirement for this action on this application."[231]

349. Because the 2000 Approval failed to meet any of the qualifications for a waiver, *see* 21 U.S.C. § 355c(a)(5)(A), (B), the FDA lacked authority when waiving the pediatric study requirement without explanation, and the 2000 Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right when the FDA waived the pediatric study requirement without explanation. For the same reason, the 2000 Approval was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law when the FDA waived the pediatric study requirement without explanation.

350. In 2016, despite contrary evidence in the administrative record, the FDA sought to provide an impermissible post-hoc rationalization that it inaccurately stated in the 2000 Approval that it was "waiving" the pediatric study requirements and, instead, should have said it had found that the requirements

[231] Ex. 25, 2000 Approval Letter at 3.

were met for post-menarchal pediatric patients by extrapolating from studies of adult populations.[232]

351. In addition to such a post-hoc rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the FDA lacked authority under PREA. The 2000 Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and the 2000 Approval was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. Because the agency was allowed to extrapolate from studies of adult populations *only if* the course of a "disease" is substantially similar in adults and the pediatric population. Because pregnancy is not a disease, PREA did not permit the FDA to make such an extrapolation.

352. In addition to such a rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the FDA lacked authority under PREA. The 2000 Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and the 2000 Approval was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law because the FDA failed to satisfy the requirement for documentation of the scientific data that supports its extrapolation that the course of the "disease" and the effects of the drug are sufficiently similar in adult women and pediatric girls.

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[232] Ex. 27, 2016 Petition Denial at 29.

353. In addition to such a rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the FDA lacked authority under PREA, the 2000 Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and the 2000 Approval was arbitrary, capricious, an abuse of discretion, and not in accordance with law because PREA allows the agency to extrapolate from adequate and well-controlled studies in adults and, as discussed above, the U.S. Clinical Trial did not include adequate and well-controlled studies in adults.

354. In addition to such a rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the 2000 Approval was arbitrary, capricious, and an abuse of discretion because the FDA's explanation that it expected girls—under the age of 18 years and going through reproductive development—to have the same physiological outcome with the drug regimen as adult women was unreasonable and not supported by the administrative record.

355. In addition to such a rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the 2000 Approval was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law because the FDA did not require an assessment that evaluated the safety and effectiveness of the drug for girls under 18 years of age.

356. Therefore, Defendants lacked the authority to approve mifepristone for chemical abortion under PREA, and the 2000 Approval was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with PREA.

IV. Pretext

357. The FDA's illegal and unreasonable rationales for the 2000 Approval—in light of the political context of the agency's actions—indicate that the stated reasons for the 2000 Approval are pretext. Therefore, the FDA's 2000 Approval is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

V. Reopener and Request

358. "The reopening doctrine . . . create[s] 'an exception to statutory limits on the time for seeking review of an agency decision.'" *Nat'l Ass'n of Reversionary Prop. Owners v. Surface Transp. Bd.*, 158 F.3d 135, 141 (D.C. Cir. 1998). "Under the reopening doctrine, the time for seeking review starts anew where the agency reopens an issue." *Sierra Club v. EPA*, 551 F.3d 1019, 1024 (D.C. Cir. 2008). The U.S. Court of Appeals for the Fifth Circuit has adopted the "reopening doctrine." *See Texas v. Biden*, 20 F.4th 928, 951–55 (5th Cir. 2021), *rev'd on other grounds*, *Biden v. Texas*, 142 S. Ct. 2528 (2022).

359. The FDA's 2016 Major Changes decision and the 2021 Petition Response reopened the FDA's underlying 2000 Approval of chemical abortion drugs for chemical abortion. When issuing these decisions, the FDA undertook a serious, substantive reconsideration of the safeguards required in the 2000 Approval decision and affirmed in the 2016 Petition Denial. Ultimately, by removing these

safeguards, the FDA completely changed the regulatory context and created a different regulatory construct for chemical abortion drugs.

360. For the reasons stated above, the FDA's 2000 Approval of chemical abortion drugs must be held unlawful, set aside, and preliminarily and permanently enjoined.

CLAIM TWO

2016 PETITION DENIAL

**ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706)
IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT;
ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW**

361. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

362. The 2002 Citizen Petition provided the FDA with substantial legal arguments that the 2000 Approval exceeded the agency's authority and was not in accordance with law under Subpart H, the FFDCA, and the Pediatric Rule.

363. The 2002 Citizen Petition also provided the FDA with significant scientific and factual reasons to withdraw the 2000 Approval.

364. By disregarding the arguments, facts, and reasons set forth in the 2002 Citizen Petition, the FDA's 2016 Petition Denial was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right; and it was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. The FDA's 2016 Petition Denial was unreasonable and not supported by the administrative record.

365. The FDA's illegal and unreasonable rationales for the 2016 Petition Denial—in light of the political context of the agency's actions—indicate that the stated reasons for the 2016 Petition Denial are pretext. Therefore, the FDA's 2016 Petition Denial is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

366. "The reopening doctrine . . . create[s] 'an exception to statutory limits on the time for seeking review [of an agency decision].'" *Surface Transp. Bd.*, 158 F.3d at 141. "Under the reopening doctrine, the time for seeking review starts anew where the agency reopens an issue." *Sierra Club*, 551 F.3d at 1024. The U.S. Court of Appeals for the Fifth Circuit has adopted the "reopening doctrine." *See Texas v. Biden*, 20 F.4th at 951–55.

367. The FDA's 2016 Major Changes decision and the 2021 Petition Response have reopened the FDA's 2016 Petition Denial. When issuing these decisions, the FDA undertook a serious, substantive reconsideration of the safeguards enshrined in the 2000 Approval decision. Ultimately, by removing the safeguards in the 2000 Approval, the FDA created a different regulatory construct and completely changed the regulatory context for the chemical abortion drug regimen.

368. Therefore, the FDA's 2016 Petition Denial must be held unlawful, set aside, and preliminarily and permanently enjoined under the APA.

CLAIM THREE

2016 MAJOR CHANGES

ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706) IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT; ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

369. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

370. Defendants lacked legal authority to make the 2016 Major Changes.

I. FFDCA

371. The FDA's 2016 Major Changes violated the FFDCA because they did not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.

372. The 2016 Major Changes violated the FFDCA because the results of the tests on which the FDA relied for its 2016 Major Changes showed that chemical abortion is unsafe for use under such conditions, or they did not show that such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.

373. The 2016 Major Changes violated the FFDCA because the FDA had insufficient information to determine whether mifepristone is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.

374. The FDA's 2016 Major Changes lacked substantial evidence that the new drug will have the effect it purports or is represented to have under the

conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.

375. In violation of the FFDCA, none of the studies on which the FDA relied for its 2016 Major Changes evaluated the safety and effectiveness of the chemical abortion regimen under the conditions of the label approved in 2016, or they failed to satisfy the substantial evidence requirement for showing the safety and effectiveness of the regimen under the conditions of the label approved in 2016.

376. Therefore, Defendants lacked legal authority to make the 2016 Major Changes. The FDA's 2016 Major Changes were in excess of statutory jurisdiction, authority, or limitations, or short of statutory right under the FFDCA. The FDA's 2016 Major Changes were unreasonable and not supported by the administrative record.

II. PREA

377. The FDA lacked legal authority under PREA to make the 2016 Major Changes, and the 2016 Major Changes were in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and were arbitrary, capricious, an abuse of discretion, and not in accordance with law, because PREA allows the FDA to extrapolate from studies of adult populations only if the course of a "disease" is substantially similar in adults and the pediatric population. Because pregnancy is not a disease, PREA did not permit the FDA to make such an extrapolation.

378. Defendants lacked legal authority under PREA to make the 2016 Major Changes and the 2016 Major Changes were in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and were arbitrary, capricious,

an abuse of discretion, and not in accordance with law, because the FDA failed to satisfy the requirement for documentation of the scientific data that supports its extrapolation that the course of the "disease" and the effects of the drug are sufficiently similar in adult women and pediatric girls.

379. Defendants lacked legal authority under PREA to make the 2016 Major Changes and the 2016 Major Changes were in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and were arbitrary, capricious, an abuse of discretion, and not in accordance with law, because the FDA did not require an assessment that evaluated the safety and effectiveness of mifepristone for girls under 18 years of age.

III. Pretext

380. The FDA's illegal and unreasonable rationales for the 2016 Major Changes—in light of the political context of the agency's actions—indicate that the stated reasons for the 2016 Major Changes are pretext. Therefore, the FDA's 2016 Major Changes is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

IV. Request

381. For the reasons stated above, the FDA's 2016 Major Changes must be held unlawful, set aside, and preliminarily and permanently enjoined.

CLAIM FOUR

2019 ABBREVIATED NEW DRUG APPROVAL

**ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706)
IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT;
ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW**

382. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

383. Defendants lacked legal authority to issue the 2019 ANDA Approval.

384. Because the FDA relied on the unlawful 2000 Approval of Mifeprex as a means to approve GenBioPro's generic drug, Mifepristone Tablets, 200 mg, if the Court finds that the 2000 Approval was unlawful, as set forth above, then the 2019 ANDA Approval needed independently to satisfy the requirements of the FFDCA and PREA.

385. Unable to rely on an unlawful approval, the FDA's approval of the 2019 ANDA Approval violated the FFDCA because it lacked the clinical investigations, adequate testing, sufficient information, and substantial evidence to show the safety and effectiveness of mifepristone under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof as required by 21 U.S.C. § 355(d).

386. Unable to rely on an unlawful approval, the FDA's approval of the 2019 ANDA also violated PREA because the submission lacked the necessary assessment on the safety and effectiveness of mifepristone on the pediatric population as required by 21 U.S.C. § 355c(a).

387. For these reasons, the 2019 ANDA Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and the 2019 ANDA Approval was arbitrary, capricious, an abuse of discretion, and not in accordance with law.

388. The FDA's illegal and unreasonable rationales for the 2019 ANDA Approval—in light of the political context of the agency's actions—indicate that the stated reasons for the 2019 ANDA Approval are pretext. Therefore, the FDA's 2019 ANDA Approval is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

389. Therefore, the 2019 ANDA Approval must be held unlawful, set aside, and preliminarily and permanently enjoined.

CLAIM FIVE

2000 APPROVAL, 2016 MAJOR CHANGES, 2019 ANDA APPROVAL, 2021 NON-ENFORCEMENT DECISION, AND 2021 PETITION RESPONSE

***ULTRA VIRES;* ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706) IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT; ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW**

390. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

391. The FDA lacked legal authority when issuing its 2000 Approval, 2016 Major Changes, 2021 Non-Enforcement Decision, and 2021 Petition Response.

392. None of these FDA actions comply with the federal laws that expressly prohibit the mailing or delivery by any letter carrier, express company, or other

common carrier of any substance or drug intended for producing abortion. 18 U.S.C. §§ 1461–62.

393. Since the 2000 Approval, the FDA has failed to restrict the upstream distribution of chemical abortion drugs from manufacturer or importer to abortionists in violation of these federal laws.

394. The FDA's 2021 Non-Enforcement Decision and 2021 Petition Response also violated these federal laws because they impermissibly removed the in-person dispensing requirement for chemical abortion drugs and, accordingly, authorized the downstream distribution of chemical abortion drugs by mail, express company, and other common carriers.

395. Because a federal agency cannot permit what federal law expressly prohibits, the FDA lacked legal authority when issuing its 2000 Approval, 2016 Major Changes, 2021 Non-Enforcement Decision, and 2021 Petition Response.

396. Therefore, the FDA's 2000 Approval, 2016 Major Changes, 2021 Non-Enforcement Decision, and 2021 Petition Response must be held unlawful, set aside, and preliminarily and permanently enjoined under the Court's inherent equitable power to enjoin *ultra vires* actions, *Larson*, 337 U.S. at 689–91.

CLAIM SIX

2021 PETITION RESPONSE

ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706) IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT; ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

397. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

398. The 2019 Citizen Petition provided the FDA with significant data and reasons to justify restoring the pre-2016 REMS.

399. The 2019 Citizen Petition also provided the FDA with significant data and reasons to justify strengthening the REMS for chemical abortion drugs, including the requirement that the abortionist uses an ultrasound to assess gestational age and diagnose ectopic pregnancies.

400. Finally, the 2019 Citizen Petition asked the FDA to require a formal study of outcomes for at-risk populations, including girls under the age of 18 years, as the agency has never studied these outcomes.

401. By disregarding the data and reasons set forth in the 2019 Citizen Petition, the FDA's 2021 Petition Response was unreasonable and not supported by the administrative record.

402. The FDA's 2021 Petition Response was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right and arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law.

403. The FDA's illegal and unreasonable rationales for the 2021 Petition Denial—in light of the political context of the agency's actions—indicate that the stated reasons for the 2021 Petition Denial are pretext. Therefore, the FDA's 2021 Petition Denial is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

404. Therefore, the FDA's 2021 Petition Response must be held unlawful, set aside, and preliminarily and permanently enjoined under the APA.

PRAYERS FOR RELIEF

For these reasons, Plaintiffs respectfully request that the Court enter an order as to Defendants, including their employees, agents, successors, and all persons in active concert or participation with them.

A. Issue a preliminary and permanent injunction ordering Defendants to withdraw mifepristone and misoprostol as FDA-approved chemical abortion drugs and to withdraw Defendants' actions to deregulate these chemical abortion drugs.

B. Hold unlawful, set aside, and vacate the 2000 Approval.

C. Hold unlawful, set aside, and vacate the 2016 Petition Denial.

D. Hold unlawful, set aside, and vacate the 2016 Major Changes.

E. Hold unlawful, set aside, and vacate the 2019 ANDA Approval.

F. Hold unlawful, set aside, and vacate the 2021 Non-Enforcement Decision.

G. Hold unlawful, set aside, and vacate the 2021 Petition Response.

H. Declare that the chemical abortion drugs mifepristone and misoprostol fall outside the scope of the FDA's regulation entitled "Subpart H–Accelerated

Approval of New Drugs for Serious or Life-Threatening Illnesses" (codified at 21 C.F.R. §§ 314.500, et seq.) because pregnancy is not an "illness" and these drugs do not "provide meaningful therapeutic benefit to patients over existing treatments."

I. Declare that the Federal Food, Drug, and Cosmetic Act requires the FDA to rely on clinical investigations and studies that show a drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof when reviewing and approving a new drug application or a supplemental new drug application.

J. Declare that the Federal Food, Drug, and Cosmetic Act prohibits the FDA from relying on studies that incorporate safeguards and protections not included under the conditions prescribed, recommended, or suggested in the proposed labeling when reviewing and approving a new drug application or a supplemental new drug application.

K. Declare that the Federal Food, Drug, and Cosmetic Act prohibits the FDA from relying exclusively on studies that fail to evaluate all the requested changes in the proposed labeling thereof when reviewing and approving a new drug application or a supplemental new drug application.

L. Declare that 18 U.S.C. § 1461 and 18 U.S.C. § 1462 prohibit the FDA from approving a new drug application or a supplemental new drug application that fails to limit distribution of chemical abortion drugs in accordance with these laws.

M. Retain jurisdiction of this matter for the purpose of enforcing this Court's order.

N. Award Plaintiffs' costs, attorneys' fees, and other disbursements for this action.

O. Grant any other relief this Court deems equitable, just, and appropriate.

Respectfully submitted this November 18, 2022.

By: s/ *Erik C. Baptist*

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**Pro Hac Vice Application forthcoming*

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 28, 2000

FROM: /S/

SUBJECT:

TO: NDA 20-687 MIFEPREX (mifepristone) Population Council

This memo documents the approval action concerning the Population Council's NDA for mifepristone for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The application was initially submitted to the Food and Drug Administration (FDA) on March 14, 1996. The Reproductive Health Drugs Advisory Committee met on July 19, 1996 and voted that benefits exceeded risk for this drug product with 6-yes, 0-no, and 2 abstentions. An approvable action letter was issued September 18, 1996 citing deficiencies in areas of Clinical (distribution system), Chemistry/Manufacturing and Controls, Biopharmaceutics, and Labeling. A complete response was received August 18, 1999. The last action by the Office was on February 18, 2000. That approvable action letter listed application deficiencies consisting of Chemistry/Manufacturing and Controls, Labeling, and the Distribution System issues. The Population Council submitted a complete response on March 30, 2000. After a brief summary of effectiveness and safety, this memo addresses those outstanding issues listed in the last action letter, Phase 4 commitments, and other issues.

Summary of Effectiveness and Safety

Effectiveness and safety data were derived from one U.S. clinical trial and two French trials. Effectiveness was defined as the complete expulsion of products of conception without the need for surgical intervention.

The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period. Demographic data showed racial composition of the U.S. trial was similar to the overall U.S. general population. Medical abortion was complete in 92.1% of 827 subjects. Surgical intervention was performed in 7.9% of subjects: 1.6% had medically indicated interventions (1.2% for heavy bleeding), 4.7% had incomplete abortions, 1.0% had ongoing pregnancies, and 0.6% had intervention at the patient's request. One of the 859 patients received a blood transfusion.

The two French trials enrolled a total of 1,681 women providing effectiveness outcomes and 1,800 women providing safety information. Medical abortion was complete in 95.5% of the 1681 subjects. Surgical intervention was performed in 4.5% of subjects: 0.3% for bleeding, 2.9% for incomplete abortions, and 1.3% for ongoing pregnancies. Of the 1,800 women, 2 patients received blood transfusions.

The Advisory Committee reviewed the French data in 1996 and voted 6-yes and 2-no for data supporting efficacy, 7-yes and 1-abstention for data supporting safety. As stated above, the overall vote for benefits exceeding risk was 6-yes, 0-no, and 2-abstentions. During the second review cycle in 1999, the committee received a copy of the U.S. study report, as they requested, to provide FDA with comments. None were received. The U.S. trial data confirms the effectiveness and safety of the product.

Chemistry/Manufacturing

In May, 2000 the Population Council informed the Division of Reproductive and Urologic Drug Products that the bulk drug substance maker had changed manufacturing processes last summer. New analytic, physical, and stability data were received and reviewed and found to be adequate to ensure the quality of the drug manufacturing was preserved.

An inspection of the bulk drug substance maker was performed on July 24-28, 2000. Deficiencies were cited and the manufacturer corrected these. These corrections were found acceptable.

Because the drug is being distributed directly to qualified physicians, there is minimal chance for drug name confusion and I agree with the name, Mifeprex.

Labeling

Labeling is important to educate prescribers and patients about the safe and effective use of the drug and to inform health professionals about adverse event risks. The 1996 Advisory Committee strongly supported education of users of mifepristone. By coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic pregancies (and other requirements), goals of safe and appropriate use may be achieved. The drug's labeling is now part of a total risk management program that will be summarized below. The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement will together constitute the approved product labeling to ensure any future generic drug manufacturers will have the same risk management program.

The labeling for mifepristone has been revised to provide information about how to report adverse events. FDA and the Population Council agree that a black box will highlight special items related to the drug. In addition, FDA has determined that a Medication Guide for this drug will help ensure dispensers provide important information to patients to enhance compliance with the regimen for safety and efficacy. Furthermore, a patient agreement fosters active patient education and participation in this regimen. The Population Council will provide these educational materials (the professional labeling, the Medication Guide, the patient agreement form, and the Prescriber's Agreement form). The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement must be read, understood, and attested to by physicians who meet prescribing qualifications (discussed below).

Black Box

21 CFR 201.57(e) permits FDA to require a black box warning for special problems, particularly those that may lead to death or serious injury. The Population Council agreed in its July 5, 2000 submission to a black box warning. It was agreed that the box would contain the following:

> "If Mifeprex results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions of whom to call and what to do in the event of an emergency following administration of Mifeprex.
>
> Prescribers should make sure the patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement."

Misoprostol Administration

The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. The data were anecdotal off-label experience with

a vaginal misoprostol regimen, an observational study about home use in Guadeloupe, and a U.S. clinical study of home use of a different regimen with different drug doses. The only study that commented on whether home use led to correct use was the Guadeloupe study reporting that 4% of patients who took misoprostol at home did it incorrectly. Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.

Early in drug development, a mandatory observation period of 3-4 hours was instituted in clinical trials worldwide when a prostaglandin analogue, sulprostone, was used with mifepristone and felt to have some cardiovascular risk. This drug is no longer being used with mifepristone and is not a marketed drug in the U.S.; therefore, the rationale for an observation period is moot. There is no more likelihood of an adverse event occurring in the few hours after misoprostol administration than during the entire study period.

Therefore, as a consequence of this re-evaluation, the labeling currently reads that the patient returns on Day 3 for misoprostol and is given instructions about adverse events and whom to contact for questions and emergencies.

Access to Health Care and Emergency Services

FDA agreed with the Population Council that access to health care and emergency services is critical for the safe and effective use of the drug. The clinical trials ensured access to services. The labeling has a black box highlighting the possible need for surgical intervention and either the provision of access to these services by the prescriber or through referral. The labeling has a contraindication if there is no access to medical facilities for emergency services. The Patient Agreement emphasizes the need to know what to do in the case of an emergency.

Patient Agreement Form

Patients should be informed about the indication of the drug and how it is given. They must understand the type of regimen they are about to commit to and its risks and benefits. The signed agreement form will be given to the patient for her reference and another kept in the medical record. The Population Council has committed to auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms.

Biopharmaceutics

This review cycle, the clinical biopharmaceutical reviewers evaluated new data in the published literature regarding the metabolism of mifepristone by the P450 3A4 system. Mifepristone is a substrate and this may inhibit drug metabolism of certain drugs and induce metabolism of others. This information was placed in the professional labeling and patients are instructed in the Medication Guide that use of other drugs may interfere with actions of mifepristone and misoprostol.

Pharmacology-Toxicology

Current literature on the effects of human fetal exposure to mifepristone and misoprostol or mifepristone alone was reviewed to ensure risk information was current. Many of the case reports of malformation concern the unsuccessful use of misoprostol for abortion, resulting in limb, facial, cranial, and other abnormalities. Many reports were retrospective in nature, subject to reporting and recall bias. Nevertheless, the risk of malformation is very important to address. This drug's indication is for pregnancy termination. The labeling, Medication Guide, process of obtaining patient agreement on medical abortion, and the commitment of the physicians through their signed Prescriber's Agreement are all meant to ensure women are completely informed about the process and make a commitment to follow through.

The labeling for Mifeprex states that it is used with misoprostol for termination of pregnancy of 49 days or less. Human data on mifepristone and misoprostol used in this timeframe is available. Safety Update Report #3 submitted on March 31, 2000 contains [redacted] Periodic Safety Update Report #9 for the period of September 1, 1998 to November 30, 1999. It lists 38 on-going pregnancies with mifepristone plus misoprostol. The Lancet published a letter in July 1998 from [redacted] in which they mention that they had reviewed 71 cases of continuing pregnancies after failed early termination of pregnancy occurring from 1987 to 1998 and found no reported cases of malformation associated with use of mifepristone and misoprostol. There was one report of sirenomelia and cleft palate in a patient who had a therapeutic termination at week 7 gestation associated with mifepristone use alone. On July 6, 1999 the European Summary of Product Characteristics contains a statement for mifepristone that in humans, the reported cases do not allow a causality assessment for mifepristone alone or used with a prostaglandin. On August 21, 2000 the sponsor provided [redacted] 12/1/99 to 5/31/00 Periodic Safety Update on pregnancy outcomes following early pregnancy exposure. The current labeling has these new data on 82 pregnancies exposed to mifepristone only (40) and mifepristone used with misoprostol (42). FDA agrees that no conclusion can be made from the data at this time. Information on the possibility of a risk of malformation, including the above information as well as the anecdotal reports, is nevertheless included in the professional labeling, Medication Guide, and Patient Agreement. The Population Council has committed to continuing ongoing surveillance of human malformation risk.

Medication Guide

This product will be approved with a Medication Guide which dispensers must provide with the drug. It is important for patients to be fully informed about the drug, as well as the need for follow up, especially on Day 14 to confirm expulsion. A Medication Guide was determined to be necessary to patients' safe and effective use of the drug. The drug product is important to the health of women and the Medication Guide will encourage patient adherence to directions for use. Patient adherence to directions for use and visits is critical to the drug's effectiveness and safety.

Distribution System

Since 1996, FDA and the Population Council have agreed, as publicly discussed with the Reproductive Drug Products Advisory Committee, that once approved, the drug will be distributed directly to physicians. It will not be available from pharmacies. There were also discussions about the qualifications of the physicians receiving mifepristone for dispensing. The Committee also stated it was important that women have access to medical abortion as this new therapeutic option may offer women avoidance of a surgical procedure.

In January 2000, the Population Council provided its initial plan for drug distribution. This plan was resubmitted in its complete response of March 30, 2000. This plan had acceptably addressed the issue of physical security of the drug. The distribution system plan stated specific requirements imposed on and by distributors of the drug, including procedures for storage, dosage tracking, damaged product returns, and other matters. See Subpart H of this memo for more details. Other aspects of the distribution system are addressed below.

Physician Qualifications

Physician qualifications were discussed within CDER, the Agency, and with the Population Council. FDA also discussed physician qualifications with a special government employee with expertise in early pregnancy. The Population Council proposed that the drug be directly distributed to qualified physicians, as opposed to other types of health care professionals (midwives, physician's assistants, nurse practitioners, etc.). This restriction was supported by the discussions of the 1996 Advisory Committee. In fact, the clinical trial data was derived from the experience of physicians using this drug. Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician, from

dispensing the drug to patients, provided state laws permit this. Should data be provided to amend the restriction to physicians, FDA will consider them.

The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and/or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists. All patients were within one hour of emergency facilities or the facilities of the principle investigator.

The role of ultrasound was carefully considered. In the clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, dating pregnancies occurs through using other clinical methods, as well as through using ultrasound. Ultrasound information can be provided to the prescribing physicians to guide treatment, but this information can be obtained through consultation referral from an ultrasound provider and does not necessarily need to be obtained by the prescriber him/herself. The labeling recommends ultrasound evaluation as needed, leaving it to the medical judgement of the physician.

The Population Council proposed that any physician who could date pregnancies and diagnose ectopic pregnancies should be able to receive the drug from the distributor. These two qualifications alone limit the number of physicians who will be eligible to receive mifepristone from the Population Council's distributor(s) to those physicians who are very familiar with managing early pregnancies. These two qualifications also are performance-based standards and do not limit providers of mifepristone to specific medical subspecialties. Education about the use of the drug is described above in the Labeling section of this memo. Because qualified physicians will be using this drug, there is no need for special certification programs. The current labeling and distribution system states physician need not have skills for handling surgical interventions, but could provide referral to services for incomplete abortion and emergency care. The Population Council stated that current medical practice is structured on referral of patients who need surgery (for example, women with a spontaneous incomplete abortion or a cardiologist's patient who needs by-pass grafts) to a physician possessing the skills to address the problem. Moreover, within the U.S. clinical trial, 11 patients out of roughly 850 patients needed surgical intervention to handle bleeding, the most important urgent adverse event associated with this drug, and 3 of these patients were handled by non-principal investigators such as the emergency room and non-study gynecologist. This suggests that patients will get the needed surgical intervention by either their physician or another physician with the needed skills. Referral to a hospital for emergency services does not mean having admitting privileges, but having the ability and the responsibility to direct patients to hospitals, if needed. The professional labeling and the Medication Guide highlight that surgery may be needed and patients need to know if the provider of mifepristone will furnish surgical intervention or if the patient will be referred. If the latter, the treating health care provider must give the patient the name, address, and phone number of this referred provider. To ensure that the quality of care is not different for patients who are treated by physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study. This monitoring study incorporates study questions of four of the original six Phase 4 commitments. See Phase 4 Commitments for additional information.

Finally, the one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services. This concern has been dealt with through the labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated.

Subpart H

In the February 18, 2000 approvable letter, FDA stated that the eventual approval of this drug would be under Subpart H. (21 CFR 314.500-314.560). This subpart applies to certain new drugs that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. FDA has determined that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H. The meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure. Subpart H applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with special skills or experience. In the case of mifepristone, the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications. Under 21 CFR 314.520, distribution of mifepristone is restricted as described below.

- Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately
  - Ability to diagnose ectopic pregnancies
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
  - Has read and understood the prescribing information of Mifeprex
  - Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
  - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
  - Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
  - Must record the Mifeprex package serial number in each patient's record

- With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:
  - Secure manufacturing, receiving, and holding areas for the drug
  - Secure shipping procedures, including tamper-proof seals
  - Controlled returns procedures
  - Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
  - Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
  - Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

The Population Council agreed to approval under Subpart H in their letter of September 15, 2000.

Phase 4 Commitments

In 1996, the Population Council committed to 6 post-marketing studies: 1) to monitor the adequacy of the distribution and credentialing system; 2) to follow up on the outcome of a representative sample of mifepristone treated women who have surgical abortion because of method failure; 3) to assess the long term effects of multiple use of the regimen; 4) to ascertain frequency with which women follow the complete treatment regimen and the outcome of those who do not; 5) to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke; 6) to ascertain the effect of the regimen on children born after treatment failure.

During this review cycle, items 1, 2, 4 and 5 were revised and integrated into a monitoring study to ensure providers who did not have surgical intervention skills and referred patients for surgery had similar patient outcomes as those patients under the care of physicians who possessed surgical skills (such as those in the clinical trial). This study specifically addresses adequacy of qualifications (#1). FDA reviewed the protocols from the Population Council submitted on September 7, 2000 and provided a revised protocol on September 13, 2000 in which the investigators collect data on safety outcomes (#2), return for their follow up visits (#4), and include all ages (#5) and collect smoking status (#5). Commitment #2 was defined by the Advisory Committee discussions of 1996 surrounding the question of whether certain physician specialties would have higher rates of problems encountered with medical abortion. This study specifically will investigate the performance of specialties with surgical skills compared to those that refer for surgical interventions with respect to incidence of medical abortion failures.

The Population Council agrees to study ongoing pregnancies and their outcomes through a surveillance, reporting, and tracking system (#6). This protocol summary and a summary for the monitoring system was received on September 19, 2000 and both were found to be adequate.

The Population Council asked that Commitment #3 (to assess the long term effects of multiple use of the regimen) be waived because it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug, especially given privacy issues. In addition, the pharmacology of mifepristone does not suggest any carry over effect after one-time administration. The Agency agrees with this assessment.

As a note, this cycle the Population Council provided new data concerning Commitment #5 (to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke), from Spitz et al. This study had 106 women ages 35 years or older as well as 51 subjects under age 20, all of whom were 49 days or less since their last menstrual period. The data on the older women is informative and of meaningful sample size. FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Sptiz data actually suggests a trend towards increased success of medical abortion with younger patients. However, as these age groups were not part of the NDA indication and the data on safety and effectiveness were only reviewed for the indication's age group (18-35 years of age), the trials excluded patients younger than 18 years old, and the raw data from Sptiz have not been submitted for review, the labeling states the safety and efficacy in these groups have not been studied. The Population Council will collect outcomes in their Phase 4 studies of women of all ages to further study this issue. With respect to smokers, the Population Council will study smokers of various ages to collect safety information. In sum, the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996.

The postmarketing audit of signed Patient Agreement forms was discussed above.

Public Comments Considered

The Food and Drug Administration received over 1,000 letters or emails from the public about mifepristone. Most comments objected to various restrictions of the drug's distribution. For example, many letters opposed press reports of an alleged FDA public registry of doctors who dispense mifepristone. Other letters focused on the research uses of mifepristone for neurologic and oncologic diseases and the concern that restricting distribution after approval would constrain off-label uses. Still other letters expressed misunderstanding that experimental indications that are subject to INDs would be limited by an approval of mifepristone with distribution restrictions. These comments were reviewed and considered.

Risk Management Program

Risk management for a drug has the goal of optimizing the use of a product by maximizing its benefits and minimizing its risks. Interventions to manage risk include education to physicians, patients, and the public, labeling (including warnings, precautions, contraindications, dosage and administration, and Medication Guide), restriction of product use or supply, and packaging changes. This drug is being approved under Subpart H (restrictions on distribution) as part of the risk management program. The Population Council and FDA have identified the areas below, among others, that contribute to drug safety and effectiveness:

1. Proper selection of patients via physicians who are qualified to do so by dating pregnancies and diagnosing ectopics,
2. Qualified physicians to administer or supervise the administration of the medication
3. Compliance with the regimen by physicians and patients through education and monitoring
4. Safety and effectiveness information that fully informs patients and physicians about the risks and benefits of the treatment
5. Evaluation of physician qualifications through Phase 4 studies has been discussed in above sections.
6. Physical packaging in unit of dosing to ensure proper dose and provision of Medication Guide with each dose
7. Active patient participation in the treatment through the Patient Agreement and Medication Guide with an audit of signed Patient Agreement to ensure compliance
8. Active programs to get physicians to report adverse events and ongoing pregnancies to provide accurate risk information
9. Commitment to review and revise the risk management program for improved public health

All components of this risk management program have been discussed above, including the Medication Guide, the labeling that includes the Prescriber's and Patient Agreement forms, approval under Subpart H, and Phase 4 studies to evaluate risk management interventions and to gather data on risks.

In summary, all approval issues related to the NDA have been addressed adequately.

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687

SEP 28 2000

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, April 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative

purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call [redacted]

Sincerely,

/S/

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Citizen Petition

March 29, 2019

The undersigned submit this petition to request the Commissioner of Food and Drugs to: (I) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (II) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS), and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

A. Action Requested

I. RESTORE AND STRENGTHEN ELEMENTS OF THE MIFEPREX REGIMEN AND PRESCRIBER REQUIREMENTS APPROVED IN 2000.

Current language and requested language for the Mifeprex Label and the Mifeprex *Risk Evaluation and Mitigation Strategy* (REMS) are included in Exhibit A.[1] Requests include:

A. Indications and Usage. Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days' gestation.

B. Dosage and Administration.

1. Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

2. The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

C. Contraindications. Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

D. Adverse Event Reporting. Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

[1] Other documents will require corresponding modifications, including the Mifeprex Medication Guide, Prescriber Agreement Form, and Patient Agreement Form.

E. Additional studies. The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

II. RETAIN THE MIFEPREX RISK EVALUATION AND MITIGATION STRATEGY (REMS), AND CONTINUE LIMITING THE DISPENSING OF MIFEPREX TO PATIENTS IN CLINICS, MEDICAL OFFICES, AND HOSPITALS, BY OR UNDER THE SUPERVISION OF A CERTIFIED PRESCRIBER.

A. Retain the Mifeprex REMS.

B. Continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

1. Mifeprex should be dispensed only in clinics, medical offices, and hospitals.

    a. The "TelAbortion" Direct-to-Consumer Mifeprex Study

    b. The Mifeprex through Pharmacy Dispensing Study

    c. Beyond the Current Studies

2. Mifeprex Prescribers Should be Certified.

B. Statement of Grounds

I. RESTORE AND STRENGTHEN ELEMENTS OF THE MIFEPREX REGIMEN AND PRESCRIBER REQUIREMENTS APPROVED IN 2000.[2]

A. Indications and Usage. Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days' gestation.

In 2016, FDA increased the maximum gestational age for Mifeprex use for abortion from 49 days (7 weeks) to 70 days (10 weeks), and changed the method of administration of misoprostol from oral to buccal (*i.e.*, in the cheek pouch). However drug-induced abortion[3] regimens demonstrate an increase in complications and failures after 49 days' gestation.

In a 2011 study of thousands of patients, the majority of whom had a drug-induced abortion using what is now the Mifeprex regimen, the rate of infection and the rate of failure requiring surgical intervention increased with gestational age.[4] The American College of Obstetricians and Gynecologists (ACOG) has stated: "the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days."[5]

Further, a 2015 meta-analysis examined all the existing publications on buccal administration of misoprostol, 20 studies in all, from November 2005 through January 2015. The failure rate of the buccal misoprostol regimen increased as the gestational age

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[2] The FDA approved Mifeprex for use in the United States on September 28, 2000, with safeguards considered necessary to ensure patient safety. The drug's initial approval was for termination of pregnancy, in a regimen with misoprostol, through 49 days of pregnancy. FDA significantly modified the drug's label at the application of the manufacturer, Danco Laboratories, in 2016, extending approved use to 70 days of pregnancy. Additional changes included: a new dosage of both Mifeprex and misoprostol; permitting home administration of Mifeprex and misoprostol; a new route of administration for the misoprostol (buccal, in the cheek pouch); permitting non-physicians to become certified prescribers; a decrease from 3 to 1 mandatory office visits by the patient; and reduced reporting requirements. U.S. Gov't Accountability Office, GAO-18-292, Food and Drug Administration: Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts 4-7 (2018); Mifeprex Risk Evaluation and Mitigation Strategy (REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf; Mifeprex Medication Guide, https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf.

[3] The terms "Medication abortion," "medical abortion," "chemical abortion," and "drug-induced abortion" [or termination of pregnancy] share the same meaning and refer to the use of abortion-inducing drugs, rather than surgery, to induce abortion. The current FDA-approved regimen uses two drugs, mifepristone (a.k.a. Mifeprex or RU-486) and misoprostol.

[4] Mentula MJ, Niinimaki M, Suhonen S, Hemminki E, Gissler M, and Heinkinheimo O, *Immediate Adverse Events after Second Trimester Medical Termination of Pregnancy: Results of a Nationwide Registry Study,* Human Reproduction 26(4), 927-932 (2011).

[5] ACOG Practice Bulletin 143: *Medical Management of First-Trimester Abortion*, p. 5 (Mar. 2014, reaffirmed 2016).

increased, especially at gestational ages greater than 49 days.[6] The current FDA label also acknowledges this fact.[7]

Given the serious risks of failure, hemorrhage, infection, and ongoing pregnancy that increase as pregnancy advances, the gestational limit for the Mifeprex regimen should have never been increased.

B. Dosage and Administration.

1. Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

The 2000 Mifeprex regimen required Mifeprex to be "provided by or under the supervision of a *physician*" who meets qualifications discussed in this section below.[8] However, the 2016 regimen replaced "physician" with "healthcare provider," thus permitting non-physicians to apply to be certified prescribers.[9] Given the regimen's serious risks, the FDA should limit the ability to prescribe and dispense Mifeprex to qualified, licensed physicians. Physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age.

The current Mifeprex Risk Evaluation and Mitigation Strategy (REMS), discussed in Section II below, continues to provide that "Mifeprex must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, *by or under the supervision of a certified prescriber*."[10] Yet, abortion providers today are promoting and performing "telemedicine abortions," where the certified prescriber's "supervision" of the dispensing of Mifeprex is limited to a videoconference.[11] This practice demonstrates a flagrant disregard for FDA safeguards.

To ensure true supervision, the FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex. This requirement would be consistent with other requirements in the Mifeprex Label and REMS.

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[6] Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21.
[7] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[8] Mifeprex 2000 label, Dosage and Administration, emphasis added.
[9] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[10] Mifeprex 2016 REMS, emphasis added, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf.
[11] *See* Planned Parenthood Releases New Educational Video on Telemedicine Abortion (Feb. 6, 2018), https://www.plannedparenthood.org/about-us/newsroom/press-releases/planned-parenthood-releases-new-educational-video-on-telemedicine-abortion.

In the Mifeprex Label, the FDA emphasizes that "Mifeprex is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)" because of the drug's "risks of serious complications." In a bold-print box, the FDA states that before prescribing Mifeprex, a provider must inform a patient: about the risks of serious events; whom to call and what to do if certain symptoms occur; and to take the Medication Guide with her if she visits an emergency room or healthcare provider who did not prescribe Mifeprex, so that she receives appropriate, informed care.[12]

Further, a provider must sign a Provider Agreement Form, attesting that he or she can:

- **Assess the duration of pregnancy accurately.**[13] Failures and complications of Mifeprex abortion increase with increasing gestational age. Mifeprex use is approved through 70 days' gestation.[14] FDA should strengthen this requirement by mandating that gestational age be accurately assessed by ultrasound in order to both ensure compliance with FDA restrictions and adequately inform the patient of gestational age-specific risks, which rise with increasing gestational age.

- **Diagnose ectopic pregnancies**[15] (*i.e.,* extrauterine pregnancy; pregnancy outside the uterus), which Mifeprex cannot end. When an ectopic pregnancy progresses, it can rupture the fallopian tube, causing bleeding, severe pain, or death. If a woman with an extrauterine pregnancy is given Mifeprex, she may believe the symptoms for ectopic pregnancy are simply the side effects of drug-induced abortion, which are similar. As of December 31, 2017, at least 97 women with ectopic pregnancies in the United States had been given Mifeprex.[16] Of these women, at least two bled to death from an undiagnosed ectopic pregnancy.[17] They likely did not recognize that their cramps, abdominal pain, and perhaps vaginal bleeding were dangerous—not side effects expected in a Mifeprex abortion.[18]

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[12] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[13] Mifeprex Prescriber Agreement Form, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf.
[14] *See* Section I.A, *supra.*
[15] Mifeprex Prescriber Agreement Form, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf.
[16] Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2017, RCM # 2007-525, NDA 20-687, https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM603000.pdf).
[17] *Id.*
[18] Donna Harrison, M.D. & Michael J. Norton Testimony before the Iowa Board of Medicine, p. 3 (Aug. 21, 2013), *citing* Postmarket Drug Safety Information for Patients and Providers, Questions and Answers on Mifeprex,

- **Provide surgical intervention if needed, or has made plans to provide such care through others.**[19] He or she must assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.[20]

Clearly, a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional contraindications (*i.e.*, circumstances that make a treatment or medication *unadvisable*) to Mifeprex use. These physical contraindications include pelvic infections, ovarian masses, cardiac arrhythmias, and liver abnormalities.[21] A physician bears responsibility to diagnose and rule out contraindications prior to Mifeprex use. It is inadequate to entrust this critical care to another healthcare provider who is not trained in diagnosis. Further, a healthcare provider who is not physically accessible to a patient cannot provide adequate follow-up care to patients, as required by the FDA Mifeprex regimen.

Thirty-four states permit only physicians to prescribe Mifeprex,[22] with nineteen states requiring the provider to be physically present with the patient.[23] For example, the law in Alabama states that the physical presence and care of a physician are necessary because "the failure and complications from medical abortion increase with advancing gestational age, because the physical symptoms of medical abortion can be identical to the symptoms of ectopic pregnancy, and because abortion-inducing drugs do not treat ectopic pregnancies but rather are contraindicated in ectopic pregnancies."[24]

Lawmakers in these states recognize that abortion providers cannot diagnose contraindications and cannot adequately care for their patients through a videoconference. Fundamentally, telemedicine "may be legitimate when it comes to discrete, document-based tasks such as reading X-rays," but it "is not the standard of care when it comes to abortion or the management of miscarriage."[25]

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https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm492705.htm.

[19] Mifeprex Prescriber Agreement Form, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf.

[20] *Id.*

[21] Harrison & Norton Testimony, p. 3.

[22] Donovan MK, *Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care*, Guttmacher Policy Review, Vol. 21, p. 44 (2018).

[23] *Id.*

[24] Ala. Code § 26-23E-7.

[25] Harrison & Morton Testimony, p. 19.

2. The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

The 2016 regimen significantly diminished doctor-patient interaction. While the 2000 Mifeprex label required three patient visits with the abortion provider, women may now obtain Mifeprex at a clinic and self-administer it at home. They are no longer required to return to the clinic for the administration of misoprostol, which prevents abortion providers from ensuring that they take the drugs at the correct times. Further, providers may now "confirm" that a patient's drug-induced abortion was successful without a clinic visit,[26] increasing the threat that Rh-negative patients will not receive administration of Rhogam, which is necessary to prevent serious risks in subsequent pregnancies.

The 2016 regimen directs that patients be given or prescribed misoprostol to take 24 to 48 hours after taking Mifeprex. However, without monitoring, a patient may take misoprostol before 24 hours have passed since she consumed Mifeprex, rendering the regimen ineffective and increasing the likelihood that she will experience a failed drug-induced abortion and require surgery.

Using buccal misoprostol sooner than 24 hours after administering mifepristone leads to a significantly increased failure rate. In one study investigating the timing of buccal misoprostol after mifepristone, nearly one out of every three to four women who took buccal misoprostol shortly after mifepristone failed to abort.[27] The failure rate ranged from 27% to 31%, depending on the pregnancy gestation.[28] Given these results, the authors of this study strongly recommended that buccal misoprostol not be taken immediately after mifepristone because of the very high abortion failure rate.[29] However, with home administration of misoprostol, healthcare providers have no control over when their patients consume the drug.

A woman may also choose to swallow misoprostol rather than keep the pill between her cheek and gum for 30 minutes, converting a "buccal" administration into an "oral" administration. An oral administration of misoprostol following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy.

Further, waiting until 24 hours after Mifeprex to administer misoprostol does not guarantee success, and the failure rate of buccal misoprostol is higher than that under the 2000 regimen. A comprehensive systematic review and meta-analysis of the existing

[26] *See* Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[27] Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD, *Oral Mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study*, Contraception 76 (2007) 215-220.
[28] *Id.*
[29] *Id.*

studies of the 2016 regimen found that women who take misoprostol earlier than 48 hours after mifepristone are more likely to fail the regimen.[30]

Under the 2000 regimen, doctors were also able to provide care to patients during the most challenging and painful time in the drug-induced abortion. According to the World Health Organization, up to 90% of women will abort within 4-6 hours after taking misoprostol.[31] The 2000 regimen permitted a patient to be in a clinic for this period of time, during which she would be under the observation and care of medical personnel. This observation period is for "both patient safety and compassion. . . . This is the time when women should be in a place where their bleeding can be monitored, their vital signs can be observed by trained medical personnel, and they can receive sufficient pain medication during the most difficult part of the expulsion."[32]

Abortion complications are also more frequent when women abort at home, without the oversight of a healthcare provider. A 2018 combined retrospective and longitudinal follow-up study of complications related to induced abortion in Sweden determined that "[t]he complication frequency [of drug-induced abortion] was significantly higher among women <7 gestational weeks who had their abortions *at home*."[33]

In-person contact with a healthcare provider is critical to post-abortion care as well. Abortion providers should perform a "follow-up [physical exam] after the use of mifepristone in order to confirm abortion and rule out life-threatening infection."[34] Before FDA approved the 2016 regimen, the follow-up visit was considered "very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred."[35] In fact, the 2000 label provided that "[e]ach patient must understand the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex."[36] ACOG's current policy explains that:

> Women are not good candidates for medical abortion if they … desire quick completion of the abortion process [or] are not available for follow-up contact or evaluation….[37]

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[30] Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet.Gynecol 126 (1) July 2015 12-21.
[31] World Health Organization, *Safe Abortion: Technical and Policy Guidance for Health Systems* 45.
[32] Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015) ¶ 136.
[33] Carlsson I, Breding K, and Larsson PG, *Complications Related to Induced Abortion: a Combined Retrospective and Longitudinal Follow-up Study*, BMC Women's Health (2018) 18:158, p. 4 (emphasis added).
[34] Harrison & Norton Testimony, p. 18.
[35] Mifeprex 2000 label, Day 14: Post-Treatment Examination.
[36] Mifeprex 2000 label, Information for Patients.
[37] ACOG Practice Bulletin 143, p. 6.

In addition to ensuring for all drug-induced abortion patients that the uterus has been emptied of retained tissue and that they are not suffering from infection, the follow-up examination is particularly critical for Rh-negative patients. These patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without follow-up, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies.[38]

Nonetheless, abortion advocates strongly supported the reduction in required visits, and continue to advocate for the elimination of direct provider-patient contact. Gynuity Health Projects (an organization that "has been at the forefront of efforts to increase women's access to medical abortion in settings throughout the world")[39] has conducted at least three domestic and five international studies[40] on eliminating pelvic ultrasound or exam after drug-induced abortion. Following one study, researchers determined that "[s]emi-quantitative pregnancy tests … could be used in lieu of transvaginal ultrasound and/or serum hCG at clinic-based follow-up or by women themselves for home-based follow-up."[41]

In a more recent study, researchers asserted that the "common practice of scheduling a clinical contact after every medical abortion may not be necessary to ensure safety; enabling patients to determine for themselves whether or not a contact is needed can be a

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[38] ACOG Practice Bulletin 181*: Prevention of Rh D Alloimmunization* (Aug. 2017); and SOGC Clinical Practice Guidelines: *Prevention of Rh Alloimmunization* (No. 133, Sept. 2003).

[39] *See* Gynuity Health Projects, Medical Abortion, https://gynuity.org/programs/medical-abortion. Founded by Beverly Winikoff, M.D, M.P.H., in 2003, Gynuity outlines on its "Medical Abortion" page the organization's research projects, including efforts to: "Develop innovative service delivery systems through telemedicine; Simplify and de-medicalize medical abortion services; Expand access to medical abortion in the 1st and 2nd trimesters of pregnancy; Conduct clinical research to develop new abortion medications; Develop a 'missed menses pill'/menstrual regulation method; Develop additional clinical indications for mifepristone." Gynuity has launched a "coalition to expand access to mifepristone in the United States," co-created a "medical abortion commodities database," "introduce[d] medical abortion in new settings," "incorporate[ed] new clinical evidence into service guidelines," and "expanded medical abortion access through education and local champions."

[40] *See*, *e.g., Self-Assessment of Medical Abortion Outcome Using Serial Multi-level Pregnancy Tests* [NCT02570204] (Sept. 2015 – Dec. 2016), https://www.clinicaltrials.gov/ct2/show/NCT02570204?term=Self-Assessment+of+Medical+Abortion+Outcome+Using+Serial+Multi-level+Pregnancy&rank=1; *Exploring the Role of At-home Semi-Quantitative Pregnancy Tests for Medical Abortion Follow-up* [NCT01150279] (Aug. 2009 – May 2014), https://www.clinicaltrials.gov/ct2/show/NCT01150279?term=Exploring+the+Role+of+At-home+Semi-Quantitative+Pregnancy+Tests+for+Medical+Abortion+Follow-up&rank=1; *De-Medicalizing Mifepristone Medical Abortion* [NCT00120224] (May 2005 – Apr. 2007), https://www.clinicaltrials.gov/ct2/show/NCT00120224?term=De-Medicalizing+Mifepristone+Medical+Abortion&rank=1.

[41] Lynd K, et al., *Simplified Medical Abortion Using a Semi-Quantitative Pregnancy Test for Home-Based Follow-up,* Int J Gynaecol Obstet. 2013 May;121(2):144-8.

reasonable approach."[42] They reached this conclusion even with 26% of participants failing to provide sufficient follow-up information.[43]

Gynuity researchers also conducted a recent systematic review of existing studies on "the accuracy and acceptability of a strategy for identifying ongoing pregnancy after medical abortion treatment using a low-sensitivity pregnancy test (LSPT)." While the researchers acknowledged that "the LSPT strategy had *moderate* sensitivity for identifying ongoing pregnancy" and "the LSPT itself had a limited role in the detection of treatment failures [*i.e.*, ongoing pregnancy] in the studies," they stated that the "LSPT strategy shows promise for reducing the need for in-person follow-up after medical abortion. A range of home-based options should be validated to meet the varied needs of women and abortion providers in diverse settings."[44]

In reality, a de-emphasis on follow-up care increases risks of post-abortion complications. As discussed above, the 2000 regimen's requirement that women return approximately 14 days after ingesting mifepristone was considered necessary to ensure that all pregnancy tissue had been passed.[45] This determination is crucial, because retained pregnancy tissue can lead to continued bleeding and serious intrauterine infections. The return visit permits healthcare providers to ensure that a patient is not experiencing these or other complications from the abortion procedure, and that Rh negative patients are administered Rhogam to protect future pregnancies.

Abortion advocates argue that three clinic visits make accessing abortion-inducing drugs more difficult for patients with transportation challenges; however, as noted above, ACOG acknowledges that drug-induced abortion is *contraindicated* for patients who "are not available for follow-up contact or evaluation."[46] Surgical abortion is a better choice for these patients, because it "[d]oes not require follow-up in most cases."[47]

Drug-induced abortion is a longer process that requires more attention and care from healthcare providers. Three visits to a physician in the interest of patient safety should not be sacrificed for the convenience of healthcare providers or even their patients.

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[42] Raymond EG, et al., *Self-assessment of Medical Abortion Outcome Using Symptoms and Home Pregnancy Tests*, Contraception 97 (2018) 324-28.
[43] *Id.*
[44] Raymond EG, et al., *Low-sensitivity Urine Pregnancy Testing to Assess Medical Abortion Outcome: A Systematic Review*, Contraception (2018), https://doi.org/10.1016/j.contraception.2018.03.013 (emphasis added).
[45] Mifeprex 2000 label, Day 14: Post-Treatment Examination.
[46] ACOG Practice Bulletin 143, p. 6.
[47] *Id.*

C. Contraindications. Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

The 2000 Mifeprex Label stated:

> Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.[48]

This critical language was excluded from the 2016 Mifeprex Label. Yet, studies comparing the outcome of surgical versus drug-induced abortion "have clearly demonstrated that Mifeprex abortions have a greater risk of hemorrhage, infection, continued pregnancies, retained tissue and need for emergency reoperation than surgical abortions."[49] ACOG acknowledges that "[c]ompared with surgical abortion, medical abortion takes longer to complete, requires more active patient participation, and is associated with higher reported rates of bleeding and cramping," and has lower success rates.[50]

Drug-induced abortion is optional. If a woman does not meet the criteria necessary to use abortion-inducing drugs, then surgical abortion is still an option. For women with transportation difficulties, an abortion provider can complete surgical abortion "in a predictable period of time," and the procedure "[d]oes not require follow-up in most cases."[51]

Efforts to promote abortion-inducing drugs to women in rural areas where access to emergency medical care is scarce are detrimental to women's health. It is better for a patient in a remote region to have a surgical abortion, "which requires a single visit, and is less likely to result in serious or life-threatening complications."[52]

[48] Mifeprex 2000 label, Contraindications.
[49] Harrison Aff. ¶ 115.
[50] ACOG Practice Bulletin 143, p. 3 & Box 1.
[51] *Id.*
[52] Harrison & Norton p. 9.

D. Adverse Event Reporting. Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

The 2016 regimen dramatically reduced accountability for Mifeprex providers by limiting adverse event reporting (AER) requirements, a critical safety mechanism.[53] While prescribers were required to report any serious adverse event associated with Mifeprex under the 2000 label, they are now required to report only deaths associated with Mifeprex.

Even with the 2000 regimen requirements, collecting accurate and complete adverse event information was highly difficult. Adverse events were often not reported or were interpreted by emergency health care providers as the results of spontaneous abortion.[54] The Mifeprex label instructs prescribers to "[a]dvise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe Mifeprex, so that the provider knows that she is undergoing a medical abortion."[55] Yet, many Mifeprex prescribers violate FDA protocol, instructing their patients to lie to emergency medical personnel. The organization Aid Access instructs patients that if they need to go to an emergency room:

> You do not have to tell the medical staff that you tried to induce an abortion; you can tell them that you had a spontaneous miscarriage. Doctors have the obligation to help in all cases and know how to handle a miscarriage. The symptoms of a miscarriage and an abortion with pills are exactly the same and the doctor will not be able to see or test for any evidence of an abortion, as long as the pills have completely dissolved.[56]

Such deception prevents emergency healthcare providers from appropriately caring for their patients, and further decreases the likelihood that adverse events will be reported.

With reduced AER reporting requirements under the 2016 label, what was previously difficult is now virtually impossible. The FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events. AERs are the only objective means by which FDA has any data whatsoever on the effects of the

[53] Mifeprex 2016 label.
[54] *See* GAO-18-292, pp 24-25.
[55] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[56] Aid Access, *How do you know if you have complications, and what should you do?*, https://aidaccess.org/en/page/459/how-do-you-know-if-you-have-complications-and-what-should-you-do.

Mifeprex regimen on women, and the voluntary and minimal nature of the current AERs means that FDA has no accurate information about the actual number of women injured by drug-induced abortion, or the nature of complications caused by this drug.

After prescribing Mifeprex and misoprostol, certified prescribers should at minimum be required to report the following directly to the FDA Medwatch reporting system, copying Danco Laboratories: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications. Detailed information must also be included, such as pulse, blood pressure, temperature, pre- and post-transfusion hemoglobin/hematocrit, white blood count, number of units of blood transfused, surgeries, and any other pertinent laboratory or hospital course information, as well as emergency room and hospital discharge diagnoses.

Further, FDA should provide guidance to emergency healthcare providers and physicians responsible for treating complications so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage. The guidance should also instruct these providers on how to report adverse events.[57]

The abysmal quality of the current AERs received from Danco Laboratories shows the lack of concern that Danco has demonstrated for the safety of the women who have undergone drug-induced abortion. Responsible reporting is a fundamental safety mechanism that should not be sacrificed in the interest of convenience for abortion providers.

E. Additional Studies. The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

Mifeprex was approved for use in the pediatric population in 2000 after the FDA waived, without explanation, the requirement for studies in the pediatric population. The developmental stage of puberty involves a complex interplay of both progesterone and estrogen effects on the developing female reproductive system. The use, and especially the potential multiple use, of Mifeprex, which is a powerful progesterone blocker, is

[57] The Self-Induced Abortion Legal Team has created a document titled "Self-Induced Abortion and the Law: What Emergency Room Staff Need to Know." This document heavily emphasizes patient privacy requirements, including the penalties that healthcare providers may face if they disclose patient information. While these concerns are valid, emergency healthcare providers should also have training on public health reporting requirements and how such reporting does not violate HIPAA or other laws regarding patient privacy. *See,* https://www.sialegalteam.org.

likely to significantly impact the developing reproductive system of the adolescent female.[58] It is irresponsible to allow the continued uninvestigated use of Mifeprex in the pediatric female population[59] without requiring long-term studies on the impact of Mifeprex use on pubertal development.

More than one out of every three abortions in the U.S. is a repeat abortion.[60] The repeat use of Mifeprex has been associated in some studies with adverse reproductive health outcomes in future wanted pregnancies.[61] This concern requires further study.

The adverse events of hemorrhage, retained tissue, and infection are common after Mifeprex use. The hemorrhage is often significant enough to warrant transfusion. When patients lack access to emergency medical facilities, such complications could easily translate to deaths. Thus a study of deaths and of severe hemorrhages requiring transfusion should be done to compare outcomes in women with and without access to emergency medical facilities.

II. RETAIN THE MIFEPREX RISK EVALUATION AND MITIGATION STRATEGY (REMS), AND CONTINUE LIMITING THE DISPENSING OF MIFEPREX TO PATIENTS IN CLINICS, MEDICAL OFFICES, AND HOSPITALS, BY OR UNDER THE SUPERVISION OF A CERTIFIED PRESCRIBER.

A. Retain the Mifeprex REMS.

Mifeprex, when used for abortion, is subject to a Food and Drug Administration (FDA) *Risk Evaluation and Mitigation Strategy* (REMS) with *elements to assure safe use* (ETASU). FDA determined that the Mifeprex REMS is necessary to ensure the safety and efficacy of the drug, because it carries risks of life-threatening hemorrhage, infection, continued pregnancy, retained tissue, need for emergency surgery, and death. The approved Mifeprex regimen includes the use of another potent drug, misoprostol, which carries its own risks.

Under the Mifeprex REMS with ETASU, a healthcare provider must be certified to prescribe Mifeprex by reviewing the prescribing information and completing a

[58] Arain M, et al., *Maturation of the adolescent brain*, Neuropsychiatric Disease and Treatment, 2013:9 449-461.
[59] Because of their immaturity, minors are also less likely to understand the importance of following prescriber instruction or of recognizing when they need to seek emergency medical treatment.
[60] Jones R, et al., *Which Abortion Patients Have Had a Prior Abortion? Findings from the 2014 U.S. Abortion Patient Survey*, Journal of Women's Health, DOI: 10.1089/jwh.2017.6410 (2014).
[61] Fang L, et al., *Repeated Abortion Affects Subsequent Pregnancy Outcomes in BALB/c Mice*, PLoS ONE 7(10): e48384. doi:10.1371/journal.pone.0048384 (2012).

"Prescriber Agreement Form," attesting that they can: assess the duration of pregnancy accurately; diagnose ectopic pregnancies; and provide surgical intervention in cases of incomplete abortion or severe bleeding, or designate someone else to provide that care. Further, they must agree to follow the guidelines for use of Mifeprex.

The REMS also requires Mifeprex to "be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber." Mifeprex may not be distributed or dispensed through retail pharmacies. Also, a patient must sign a "Patient Agreement Form" and be fully informed of the risks by a certified prescriber. She must receive the Mifeprex Medication Guide, informing her that she needs a "follow-up assessment" 7 to 14 days after she has taken Mifeprex to ensure that she is well and has terminated her pregnancy.[62]

The REMS remains the lone safeguard to monitor and mitigate the risks of death and adverse events from the Mifeprex regimen. Gynuity Health Projects and researchers from the University of California, San Francisco (UCSF) obtained approval from FDA through Investigational New Drug Applications (INDs) to conduct studies that *do not* comply with the Mifeprex REMS. They intend to use the results of these studies to press for the elimination of the Mifeprex REMS.[63] [See Section II.B, below.]

The Mifeprex Medication Guide acknowledges that serious risks accompany FDA's approved regimen for drug-induced abortion, which includes the use of Mifeprex and another potent drug, misoprostol. The document improperly downplays the risks, however, stating that "*rarely*, serious and potentially life-threatening bleeding, infections, or other problems can occur following . . . medical abortion." Specifically, "in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure."[64]

In fact, the internationally used criteria for reporting complications from drugs demonstrate that complications from drug-induced abortions are common, not rare. The Council for International Organizations of Medical Sciences (CIOMS)[65] defines the word

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[62] GAO-18-292, pp 4-7 (2018); Mifeprex Risk Evaluation and Mitigation Strategy (REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf; 21 U.S.C. § 355-1; Mifeprex Medication Guide, https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf.

[63] *See* Daniel Grossman, MD, Research Protocol: *Alternative Provision of Medication Abortion via Pharmacy Dispensing*, Version #:1.3 (July 17, 2018) p. 14.

[64] Mifeprex Medication Guide, https://ww.w.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf.

[65] The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, nonprofit organization established jointly by WHO and UNESCO in 1949. Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. In 2013, the membership of CIOMS included 49 international, national, and associate member organizations, representing many of the biomedical disciplines, national academies of sciences, and medical research councils.

"rare" in adverse event reporting as an event that happens in between "1 out of 1,000" to "1 out of 10,000" uses. "Common" is the uniform term used for events that happen in between "1 out of 10" to "1 out of 100" uses.[66] Given that "about 1 out of 100 women" using Mifeprex/misoprostol require surgery, serious complications are common, not rare.[67]

Also, as discussed in Section I.C above, Mifeprex abortions carry greater risks than surgical abortions.[68] A study of over 42,000 women in Finland who had abortions from 2000 to 2006 found that "overall, medical abortion had roughly four times the rate of adverse events than surgical abortion, and hemorrhaging was experienced by 16 percent of medical abortion patients compared with 2 percent of surgical abortion patients."[69]

A combined retrospective and longitudinal follow-up study of complications related to induced abortion in Sweden published in 2018 determined that the share of complications related to drug-induced abortions at less than 12 weeks *increased* significantly during 2008-2015 without an evident cause. The increase was from 4.2% in 2008 to 8.2% in 2015, with incomplete abortion as the most common complication related to drug-induced abortions at less than 12 weeks.[70]

Abortion advocates are also attacking the REMS by advocating for mifepristone use in spontaneous miscarriage management. In a small recent study, researchers compared the efficacy and safety of using mifepristone with misoprostol for the management of early miscarriages to using misoprostol alone.[71] Notably, 6-10% of study participants had a gestational age of "4-5 weeks gestation."[72] It is not clear from the authors how participants of that gestational age could meet the published guidelines for diagnosis of non-viable pregnancy recently published by the Society of Radiologists in Ultrasound multispecialty consensus panel.[73] The panel requires the crown-rump length cutoff to 7 mm for embryos without a heartbeat and the mean sac diameter cutoff to 25 mm for

[66] CIOMS training manual on medicine safety, http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf.
[67] *See* Mifeprex Medication Guide; CIOMS training manual on medicine safety, *supra.*
[68] *See* Harrison Aff. ¶ 115; ACOG Practice Bulletin 143, p. 3 & Box 1.
[69] GAO-18-292, p. 25, *discussing* Niinimaki M, et al., *Immediate Complications after Medical Compared with Surgical Termination of Pregnancy,* Obstetrics & Gynecology, vol. 114, no. 4 (October 2009): 795-804.
[70] Carlsson I, Breding K, and Larsson PG, *Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study*, BMC Women's Health (2018) 18:158.
[71] Schreiber CA, et al, *Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss*, N Engl J Med 2018; 378:2161-70.
[72] *Id.* Table 1.
[73] Doubilet PM, Benson CB, Bourne T, et al., *Diagnostic criteria for nonviable pregnancy early in the first trimester*, N Engl J Med 2013; 369:1443–1451.

"empty" sacs, in order to minimize interventions that "interrupt a pregnancy that otherwise would have had a normal outcome."[74]

The authors admit that the study "was not powered to show differences between groups in the proportions of serious adverse events,"[75] an important consideration prior to recommending a change in spontaneous abortion management protocols. Yet, the authors incorrectly stated "such events were rare."[76] Table 3 gives a total number of serious adverse events as 3.4% for the mifepristone pretreatment group, and 2.0% for the misoprostol alone group.[77] Under the CIOMS criteria for reporting complications from drugs, discussed above, the rate of 2%-3.4% of adverse events in each study arm demonstrates clearly that adverse events are common, not rare, in both misoprostol alone and mifepristone + misoprostol miscarriage management.

Further, the Mifeprex + misoprostol arm raises a concern about the need for further study of adverse events, especially hemorrhage. Mifepristone is known to inhibit endometrial hemostasis (*i.e.*, arrest of bleeding),[78] as demonstrated by many reports of hemorrhage with transfusions reported to the FDA after use of mifepristone and misoprostol for elective abortions.[79]

Of additional concern is the vaginal route of administration of misoprostol. After reports of overwhelming sepsis following vaginal administration of misoprostol, Planned Parenthood changed the route of administration of misoprostol from vaginal to buccal,[80] with subsequent decrease in reported infections. Animal studies have demonstrated that both mifepristone[81] and misoprostol[82] can profoundly suppress innate immunity and the ability to fight infections.

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[74] Hu M, Poder L, Filly R, *Impact of New Society of Radiologists in Ultrasound Early First-Trimester Diagnostic Criteria for Nonviable Pregnancy*, J Ultrasound Med 2014; 33:1585–1588.
[75] Schreiber, *supra* p. 2168.
[76] *Id.*
[77] *Id.* p. 2169.
[78] Miech RP, *Pathopharmacology of excessive hemorrhage in mifepristone abortions*, Ann Pharmacother 2007 Dec; 41(12):2002-7.
[79] Gary MM, Harrison DJ. "Analysis of severe adverse events related to the use of mifepristone as an abortifacient." Ann Pharmacother. 2006 Feb;40(2):191-7; Food and Drug Administration "Mifepristone U.S. Postmarketing Adverse Events Summary" 2011, https://www.minnpost.com/sites/default/files/attachments/Mifeprex_April2011_AEs.pdf.
[80] Fjerstad M, Trussell J, Sivin I, Lichtenberg ES, Cullins V, *Rates of Serious Infection after Changes in Regimens for Medical Abortion*, N Engl J Med 2009; 361:145-51.
[81] Sternberg EM, Hill JM, Chrousos GP, Kamilaris T, Listwak SJ, Gold PW, Wilder RL, *Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats*, Proc Natl Acad Sci U S A. 1989 Apr;86(7):2374-8; Miech RP, *Pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii*, Ann Pharmacother. 2005 Sep;39(9):1483-8. Epub 2005 Jul 26.
[82] Aronoff DM et al., *Misoprostol impairs female reproductive tract innate immunity against clostridium sordellii*, 180 J. Immunol. 8222-8230 (2008).

Despite the clear methodological errors, including a failure to accurately diagnose fetal death according to accepted criteria as well as lack of adherence to the stated inclusion criteria, and despite the absence of power to evaluate safety, abortion advocates are calling for the routine use of mifepristone to manage spontaneous miscarriages.[83] Any change in spontaneous miscarriage management with mifepristone should require an FDA New Drug Application (NDA) with two randomized controlled trials (RCTs) comparing the arms of mifepristone and misoprostol, misoprostol alone, surgical management, and expectant management. Without blinded RCTs to evaluate not only efficacy but also safety, it is premature to remove the REMS for Mifeprex to facilitate mifepristone access for spontaneous miscarriage management.

Despite the presence of serious risks and contraindications to the Mifeprex regimen, Gynuity, the University of California, San Francisco (UCSF), and other abortion advocates want the FDA to eliminate the remaining safeguards that were enacted to ensure the safety and efficacy of Mifeprex. They are pursuing their goals through publication, advocacy, litigation,[84] and/or controversial research enabled by FDA.[85]

Further, as Section II.B below explains, lifting the REMS is only the starting point for abortion advocates.

B. Continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

1. Mifeprex should be dispensed only in clinics, medical offices, and hospitals.

The Mifeprex REMS requires that Mifeprex "be dispensed to patients only in clinics, medical offices and hospitals, by or under the supervision of a certified prescriber." That prescriber must be capable of assessing the duration of a pregnancy accurately, diagnosing ectopic pregnancies, and providing or referring for surgical intervention in cases of incomplete abortion or hemorrhaging.[86]

Abortion advocates, however, want the FDA to permit healthcare providers to prescribe Mifeprex to pregnant patients over the Internet or phone, with the drug available at pharmacies or through the mail, and through advance provision (*i.e.*, before a patient is pregnant). Eliminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls. Healthcare providers

[83] Molly Walker, *Mifepristone: Better for Managing Early Miscarriage*, Medpage Today, (June 6, 2018), https://www.medpagetoday.com/obgyn/pregnancy/73336.
[84] *Chelius v. Azar*. CIV. NO. 1:17-cv-00493-DKW-KSC (Dist. Ct. HI 2018).
[85] See Section II.B, below.
[86] Mifeprex Risk Evaluation and Mitigation Strategy (REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf.

prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs.[87] Further, as discussed above, Rh-negative patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without direct patient contact, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies.[88] [See Section I.B.2, *supra*.]

Telemedicine abortion further distances women from the practitioners responsible for caring for them, and approval by FDA would further absolve abortion providers of responsibility for the well-being of their patients. Promoting telemedicine abortion to women and adolescent girls in rural areas with limited access to healthcare is extremely dangerous—they will have little recourse if they face known and predictable emergency complications such as severe hemorrhage.[89]

Nonetheless, Gynuity Health Projects and researchers from UCSF obtained approval from FDA through Investigational New Drug Applications (INDs) to conduct studies that *do not* comply with the Mifeprex REMS. They will use the results of these studies to press for the elimination of the Mifeprex REMS.

a. The "TelAbortion" Direct-to-Consumer Mifeprex Study

Gynuity Health Projects is the sponsor of the study "Feasibility of Medical Abortion by Direct-to-Consumer Telemedicine."[90] Gynuity filed an IND with the FDA.[91] The status is listed as "recruiting," with age eligibility that includes 11-year-old children and an estimated enrollment of 1,000 participants at five locations.[92] The start date is listed as March 22, 2016, and the estimated completion date was extended from June 2018 to June 2019.

The study's brief summary states: "This pilot study is designed to obtain preliminary data on the safety, acceptability, and feasibility of direct-to-consumer telemedicine

[87] Harrison & Norton Testimony, p. 2.
[88] ACOG Practice Bulletin 181*: Prevention of Rh D Alloimmunization* (Aug. 2017); and SOGC Clinical Practice Guidelines: *Prevention of Rh Alloimmunization* (No. 133, Sept. 2003).
[89] Harrison & Norton Testimony, p. 9.
[90] (NCT02513043), https://www.clinicaltrials.gov/ct2/show/NCT02513043?term=NCT02513043&rank=1.
[91] Raymond EG, Chong E, & Hyland P, *Increasing Access to Abortion with Telemedicine*, JAMA Internal Medicine Vol. 176, N. 5 (May 2016).
[92] Hawaii – University of Hawaii Women's Options Center; Maine – Maine Family Planning; New York – Choices Women's Medical Center (active, but not recruiting according to ClinicalTrials.gov, and not listed on TelAbortion.org); Oregon and Washington – Planned Parenthood Columbia Willamette; Oregon Health and Sciences University Women's Health Research Unit. Washington State patients may also participate because an Oregon abortion provider is also licensed in Washington State. Claire Lampen, *Webcam Abortion Services Offer Crucial Access—So What's Stopping them?* Gizmodo (Apr. 17, 2018).

abortion."[93] The study's website states that "[a] TelAbortion involves all the same steps and procedures as a regular medical abortion, but you do them without going into an abortion clinic."[94]

Women who participate in the study have a video "evaluation" with the study abortion provider over the Internet, during which they can ask questions, provide medical history, and learn about the pre-abortion tests that they need. They also electronically sign consent forms for the study. Afterwards, they are required to obtain the tests and direct the reports to be sent to the study provider.

Once a patient is determined eligible, the study provider will send her a package containing Mifeprex and misoprostol, with instructions that she must follow on her own. She is also instructed to have additional tests to verify that the abortion is complete, and later have another consultation with the study provider to review the results.[95]

Obviously, a woman may *not* take the abortion drugs in the manner prescribed, nor obtain the follow-up care that is recommended. With a doctor-patient relationship limited to online chats, she has virtually no accountability or support as she navigates a complicated procedure. The responsibility of the provider of the drugs to follow up with the patient is obviated as well.

b. The Mifeprex through Pharmacy Dispensing Study

The University of California, San Francisco (UCSF) is the sponsor of the "Alternative Provision of Medication Abortion via Pharmacy Dispensing" study.[96] Daniel Grossman, M.D., with UCSF is listed as the study's "responsible party."[97] Like Gynuity, UCSF filed an IND with the FDA to obtain authorization for this study.[98] The status is listed as "recruiting," with July 2019 as the estimated completion date. The sponsors plan to recruit 300 patients at four study clinic sites and survey 50 pharmacists at associated study pharmacy sites.[99]

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[93] NCT02513043, https://www.clinicaltrials.gov/ct2/show/NCT02513043?term=NCT02513043&rank=1.
[94] TelAbortion: The Telemedicine Abortion Study: FAQs, http://telabortion.org/faq/.
[95] *Id.*
[96] NCT03320057, https://www.clinicaltrials.gov/ct2/show/NCT03320057?term=NCT03320057&rank=1; Daniel Grossman, MD, Research Protocol: *Alternative Provision of Medication Abortion via Pharmacy Dispensing*, Version #:1.3 (JUL. 17, 2018) p. 5.
[97] *Id.*
[98] In a May 2018 phone conversation with a contact for the UCSF study, she stated that the study was approved through an IND application with FDA.
[99] Grossman, pp. 5-7; 16-17.

The stated aim of the study is to "investigate the feasibility, acceptability, and effectiveness of pharmacy dispensing of Mifeprex; safety data will also be collected. . . . *The results of this study eventually could lead to changes in the Mifeprex REMS*. . . ."[100]

The sponsors intend to measure "pharmacist satisfaction with dispensing Mifeprex and the proportion of pharmacists who refuse to dispense the medication to patients." They secondarily intend to assess patient satisfaction, describe clinical outcomes, including effectiveness and adverse events, and compare pharmacists' knowledge about medication abortion before and after.[101]

Patients enroll at one of the study clinic sites on Day 1, where they choose medication abortion, have an ultrasound if one has not been done, and obtain pre-abortion counseling. They then are prescribed Mifeprex, misoprostol, and anything else necessary to be filled at the associated study pharmacy site.[102] Some patients have serum hCG measured on the day of Mifeprex administration and again around eight days later "to assess for completion of the abortion."[103] The "follow-up" for patients "may include a follow-up visit or a phone call from clinic staff approximately 7-14 days after the initial visit."[104] However, as discussed extensively above, a clinician needs to perform an exam to rule out retained tissue—even if the patient has a negative serum hCG. A phone call that "may" be placed, or fail to connect, is not enough.

Notably, "[a]ll except one of [the participating] pharmacies is [sic] located within the same building as the clinic…."[105] While UCSF is using a community pharmacy not affiliated with the University, the other three study clinic sites are using affiliated pharmacies.[106]

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[100] Grossman, p.14 (emphasis added). The sponsors dubiously assert that "pharmacy dispensing could [] help increase the number of clinicians willing and able to provide medication abortion by enabling them to avoid the associated costs and logistical challenges of stocking and dispensing the medication at their facilities." They reference a survey of Fellows of the American College of Obstetricians and Gynecologists that sought to determine if doctors not presently practicing abortion would prescribe Mifeprex if their patients could obtain the drug at a pharmacy. Fifty-four percent responded to the survey. Seventy-seven percent of respondents *do not* perform abortions and nine percent perform surgical abortions only—of those, 19% said they would prescribe Mifeprex if it could be obtained at a pharmacy, and an additional 18% said they were unsure. Based on this, the sponsors claim "the proportion of obstetrician-gynecologists providing [Mifeprex] would at least double (from 14% to 29%) "if the dispensing restriction in the REMS were removed and physicians could write a prescription for Mifeprex that could be dispensed at a pharmacy." The fact that 46 percent of the fellows surveyed did not take the time to respond, however, places this conclusion in doubt. *See* Grossman, pp. 12-14.
[101] Grossman, pp. 15-16.
[102] Grossman, p. 23.
[103] Grossman, p. 23.
[104] Grossman, p. 24.
[105] Grossman, p. 20.
[106] Grossman, pp 16-17.

While the rationale for the study states that pharmacy dispensing of Mifeprex could "help facilitate provision of medication abortion through telemedicine,"[107] the sponsors emphasize that the only difference between this study and FDA protocol "is that the patient would obtain the mifepristone directly from the pharmacist, rather than in a clinic facility."[108] In fact, the schedules for the participating pharmacists are "mapped" to "ensure that trained pharmacists are available to dispense to study participants during business hours."[109]

The following demonstrates the extensive assistance that the sponsors offer patients in obtaining the drugs from the participating pharmacies:

> [The patient] will be told that only a limited number of pharmacies are able to dispense Mifeprex and given information about how to get to the participating pharmacy (as well as the hours during which a participating pharmacist will be working, if needed). If there are any gaps in staffing at the pharmacy, the patient will be notified of the timing of those gaps in coverage before leaving the clinic via the pharmacy directions/handout. If this will be an issue for the patient, a solution will be found at the clinic before the patient leaves or she will not be enrolled in the study. Patients will be told that if they have any problems accessing the medications at the clinic, they should come back to the clinic [where they can obtain Mifeprex].[110]

While this assistance may ensure that the study does not deviate dramatically from FDA protocol, the study *certainly* does not model the experience a patient would have outside of this controlled environment—particularly a patient who obtains Mifeprex through telemedicine and has no physical contact with her prescriber.

The physical proximity of the study pharmacy sites to the study clinic sites, the probable professional associations between participating doctors and pharmacists, and the extensive assistance offered by the clinics to ensure that patients access abortion-inducing drugs at participating pharmacies, raise questions as to whether the study is fundamentally biased and will inaccurately forecast widespread behavior and experiences if the REMS is removed. Therefore, any results of the study cannot provide a justification for permitting pharmacy distribution of Mifeprex, much less abortion through telemedicine.

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[107] Grossman, p. 6.
[108] Grossman, p. 6.
[109] Grossman, p. 18.
[110] Grossman, pp. 19-20.

Further, as discussed below, eliminating the REMS to enable pharmacy dispensing of Mifeprex is only the beginning of a long-term strategy to achieve over-the-counter status for Mifeprex, further diminishing patient care and abortion provider accountability.

c. Beyond the Current Studies

A recent article by Dr. Grossman and colleagues reveals that they want Mifeprex access extended even beyond the parameters contained in their Pharmacy Dispensing study. They used an online survey to gauge women's "personal interest in and general support for three alternative methods for accessing abortion pills: (1) in advance from a doctor for future use, (2) over-the-counter (OTC) from a drugstore and (3) online without a prescription."[111]

None of the options in the survey require a healthcare provider to provide patient care comparable to even the *inadequate* care provided in the two studies discussed above. Only the first option requires a prescription from a doctor; however, the doctor would not know in advance when his patient actually becomes pregnant and chooses to use the drugs. The survey disingenuously stated that "[m]edication abortion, or the abortion pill, is a safe and effective way to terminate a pregnancy up to 10 weeks," without informing participants of a single risk associated with the regimen.[112]

Further, in a November, 21, 2018 op-ed, Dr. Grossman advocated for providing abortion pills before women are pregnant. He stated:

> The idea is simple: Give women abortion pills *before* they need them – "advance provision," as it's known – so that they can take them as soon as they discover a pregnancy. Women could get the pills from their gynecologist at the time of their annual exam, say, or the pills could be made available online.[113]

Incredibly, Dr. Grossman stated that he has "few medical concerns about handing out abortion pills in advance."[114] He asserts that evidence from advance provision research "could strengthen the case for making [abortion-inducing drugs] available without a prescription."[115]

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[111] Biggs MA, et al, *Support for and interest in alternative models of medication abortion provision among a national probability sample of U.S. women,* Contraception (2018), https://doi.org/10.1016/j.contraception.2018.10.007.
[112] *See id.*
[113] Daniel Grossman, *American women should have access to abortion pills before they need them*, Los Angeles Times (Nov. 21, 2018).
[114] *Id.*
[115] *Id.*

In addition to his failure to address all of the dangers posed by abortion-inducing drugs, Dr. Grossman does not acknowledge the risk that women will share their abortion-inducing pills with other women. While an abortion provider may screen his patient for contraindications to Mifeprex, nothing will stop his patient from giving her stored Mifeprex to a friend who is unaware that she is Rh negative, for instance, which poses health risks for future pregnancies (See section I.B.2, *supra*).

In fact, Dr. Grossman's research program has listed a study titled "Alternative Provision of Medication Abortion Via Advance Provision" on ClinicalTrials.gov, with May 2019 listed as the estimated study start date.[116] In the study, patients who are "at risk of unintended pregnancy and with a desire to avoid pregnancy will be assessed by a clinician and provided counseling on pregnancy recognition and testing, as well as how to administer [drug-induced abortion] at home." They will then receive Mifeprex and misoprostol while *not* pregnant. If/when the patient becomes pregnant and wants to take the drugs, she is instructed to contact a study clinician for an "over-the-phone assessment of eligibility" for drug-induced abortion, "including evaluation of contraindications and gestational age" before taking the drugs, and "then attend a follow-up visit with the clinician."[117] However, it is impossible for the study sponsors to truly assess the patient for contraindications, verify gestational age, prevent patients from sharing the drugs with others, or ensure that patients attend a follow-up visit.

In a 2018 Policy Review, the Guttmacher Institute also advocated for lifting the Mifeprex REMS. However, the article did not stop there. The author argues:

> [w]hile lifting the REMS on mifepristone would open new possibilities for medication abortion access, stopping there would fall short of realizing the full potential of this method, particularly when it comes to self-managed abortion care. In a self-management model, anyone who needs to terminate a pregnancy would be able to legally access mifepristone and misoprostol without a requirement to see a health care provider or pharmacist first. . . . To fully integrate self-managed medication abortion with existing abortion practices in the United States, misoprostol and mifepristone must first become available without a prescription.[118]

These recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex. In spite of the serious risks and contraindications to the Mifeprex regimen, abortion advocates will not rest until Mifeprex is available to all, without a prescription

[116] NCT03829696, https://clinicaltrials.gov/ct2/show/NCT03829696?term=NCT03829696&rank=1.
[117] *Id.*
[118] Donovan MK, *Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care*, Guttmacher Policy Review, vol. 21 (2018).

or mandatory medical management of any kind. The FDA's vigilance in protecting women from such negligence is critically important.

2. Mifeprex Prescribers Should be Certified.

The 2016 regimen requires Mifeprex prescribers to be certified as qualified. This is simply common sense—only healthcare providers qualified to prescribe an abortion-inducing drug should do so. The prescriber form attests that the healthcare provider must be able to assess pregnancy duration, diagnose ectopic pregnancy, and provide or refer for surgical intervention if necessary.

Given that drug-induced abortion is contraindicated beyond 10 weeks' gestation and when the pregnancy is not in the uterus, and that *at least* 1 out of 100 women using Mifeprex need surgery,[119] these qualifications are entirely logical. Yet, abortion advocates, ignoring the best interests of their patients, claim such restrictions are onerous.[120]

CONCLUSION

The Mifeprex REMS with ETASU remains critical for patient safety. Mifeprex carries risks of life-threatening hemorrhage, infection, continued pregnancy, retained tissue, need for emergency surgery, and death. The 2000 regimen provided significantly more protections for patients than the 2016 regimen. FDA should restore and strengthen elements of the Mifeprex regimen and provider requirements, including: limiting Mifeprex use to 49 days' gestation; requiring that Mifeprex be administered only by or under the supervision of a physically present physician; requiring three office visits by a patient who has been prescribed Mifeprex; clarifying that Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care; expanding mandatory adverse event reporting; and requiring additional studies of Mifeprex use in at-risk populations.

At the very least, FDA should not further erode patient protections. The agency should retain the Mifeprex REMS, and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

[119] Mifeprex Risk Evaluation and Mitigation Strategy (REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf.
[120] Mifeprex REMS Study Group, *Sixteen Years of Overregulation: Time to Unburden Mifeprex*, N Engl. J. Med. 376;8 (Feb. 23, 2017).

C. Environmental Impact

This petition is categorically excluded under 21 C.F.R. § 25.30.

D. Economic Impact

Available upon Commissioner's request, pursuant to 21 C.F.R. §10.30(3).

E. Certification

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners, which are unfavorable to the petition.

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UNITED STATES HOUSE OF REPRESENTATIVES
GOVERNMENT REFORM COMMITTEE

OCTOBER 2006

THE FDA AND RU-486: LOWERING THE STANDARD FOR WOMEN'S HEALTH

STAFF REPORT

PREPARED FOR THE HON. MARK SOUDER
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I. EXECUTIVE SUMMARY

This report explores the Food and Drug Administration's activities as they relate to RU-486 – the abortion pill – including the highly unusual process by which the drug was approved, the failures to ensure that the drug is dispensed as the Food and Drug Administration (FDA) requires, the subsequent illnesses, hospitalizations and deaths known to be associated with the drug and the failure to provide any meaningful restrictions despite evidence of its association with a 100% fatal septic infection.

On May 17, 2006, Congressman Mark Souder, Chairman of the Subcommittee on Criminal Justice, Drug Policy and Human Resources ("Subcommittee"), House Committee on Government Reform, convened a hearing to inquire into the safety of the FDA-approved drug Mifeprex (the trade name for mifepristone) commonly known as RU-486. The hearing was entitled, "RU-486 - Demonstrating a Low Standard for Women's Health?" The Subcommittee's hearing followed several months of investigative inquiries with the FDA after the Agency's July 2005 disclosure that four women had died of a septic infection after taking RU-486 to induce an abortion.[1]

This Subcommittee Staff Report ("Report") provides background information about RU-486, including the reasons the drug was brought to market. It also explores the allegation that FDA disregarded various statutes and rules in the RU-486 approval process, and it examines RU-486's safety record in the United States. The accumulation of safety data from "real world" use of the drug in America has allowed Subcommittee investigators to more completely grasp FDA's understanding of the risks posed by RU-486 when it approved the drug on September 28, 2000.

Based on the significant demonstrated danger this drug poses to women, the Report examines options for withdrawing this drug from the market.

II. BACKGROUND

RU-486 is the common name for mifepristone, which in the United States is marketed under the trade name Mifeprex. Shanghai HuaLian Pharmaceutical Co., Ltd.[2] of China produces the drug, which is imported and distributed by Danco Laboratories, [3] a corporate entity located in the Caribbean nation of the Cayman Islands. RU-486, Danco's sole product, [4] is approved for the

[1] FDA Public Health Advisory: Sepsis and Medical Abortion, July 19, 2005. Available at http://www.fda.gov/cder/drug/advisory/mifeprex.htm (last visited October 14, 2006).

[2] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Senator Jim DeMint (August 11, 2006) (on file with Subcommittee).

[3] *See, Foes criticize Chinese manufacture of abortion pill for U.S.*, CNN.com, (Oct. 13, 2000) at http://archives.cnn.com/2000/HEALTH/women/10/13/abortionpill.plant.ap/index.html (last visited October 10, 2006).

[4] Unlike other drug companies with multiple products that are approved by or in application before the FDA--and which therefore cooperate with the FDA to withdraw drug products when recognizable problems arise--Danco has

termination of an established pregnancy through 49 days development (LMP),[5] when used in conjunction with the prostaglandin, misoprostol.[6]

RU-486 terminates pregnancy by blocking progesterone receptors in the uterus, a hormone necessary for the maintenance of pregnancy.[7] This leads to degeneration of the uterine lining, blocking nutrition to the prenate, thus resulting in its death.[8] Mifeprex is used in combination with a prostaglandin called misoprostol, which causes contractions that expel the contents of the uterus.[9] This is an off-label use for misoprostol, which contains an FDA-mandated black-box warning against using the drug during pregnancy.[10]

Under the protocol approved by the FDA – one considerably less stringent than the agency's proposed protocol leaked to the public a few months prior to approval – if the patient is

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no other products for which it must be answerable to the FDA. *See also,* Rogoff, Natasha L, *Haven or Havoc?,* PBS Frontline, February 19, 2004 at http://www.pbs.org/wgbh/pages/frontline/shows/tax/schemes/cayman.html.

[5] FDA Approval Memo (September 28, 2000); "LMP" refers to the first day of the last menstrual period, and is the customary measure of gestational age, from approximately 14 days pre-fertilization of the conceptus.

[6] The FDA examined misoprostol to see if the deadly *Clostridium Sordellii* bacteria that killed four California women after taking RU-486 was associated with misoprostol, rather than the Mifeprex: "An FDA Public Health Advisory in mifepristone dated July 22, 2005 reported 4 cases of septic death in California following the use of mifepristone and intravaginal misoprostol for medical abortion. For this reason, DRUP [Division of Reproductive and Urologic Products] and DDRE [Division of Drug Risk Evaluation] met on July 19, 2005, to discuss searches of the AWRS database to further investigate this cluster of repo0rts. At this meeting, DDRE agreed to provide 3 consults to examine this issue… The proposed consults were as follows:

- Consult #1: Review of all reports of serious infections with misoprostol in women of childbearing age
- Consult #2: Review of all reports for suspected intravaginal products with a fatal outcome
- Consult #3: Review of all serious, unusual infections with intravaginal products."

"This review did not identify any new safety signal associated with intravaginal product administration, especially in regards to infection or pregnancy status." FDA Office of Drug Safety Postmarketing Safety Review, December 8, 2005 (on file with the Subcommittee).

The FDA also tested the manufacturing lots from which the misoprostol was distributed and eliminated that drug product as a source of contamination that would have caused the fatal *C. Sordellii* infections. *See* Marc Fischer, M.D., M.P.H., CDC, *Clostridium sordelli Toxic Shock Syndrome Following Medical Abortion*, Public Workshop on Emerging Clostridial Disease," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Available at http://www.fda.gov/cder/meeting/clostridial/fisher.pdf (last visited October 20, 2006).

[7] See., e.g., University of Chicago Department of Obstetrics and Gynecology, Information on Hormonal Imbalance, available at http://babies.bsd.uchicago.edu/endo/hormoneImbalance.htm (last visited October 10, 2006).

[8] Etienne-Emile Baulieu, "RU-486 as an Antiprogesterone Steroid: From Receptor to Contragestion and Beyond," *Journal of the American Medical Assn*. 262:13; 1808-1814 (October 6, 1989).

[9] Pfizer (along with their generic subsidiary) and Teva Pharmaceuticals, the makers of misoprostol, have never filed a New Drug Application to seek approval from the FDA for its use in abortion. It was approved for use with ulcers, and is contraindicated for pregnancy. Pfizer's German affiliate recently pulled the drug from the market.

[10] Cytotec (misoprostol) Full Revised Label, April 17, 2002, available at www.fda.gov/cder/foi/label/2002/19268slr037.pdf (last visited October 10, 2006).

found to be a candidate for a chemical abortion (according to criteria such as gestational age of 49 days or less, absence of ectopic pregnancy and a host of health contraindications), she is given 600 mg of Mifeprex to consume at once and instructed to return two days later to consume orally 400 mcg of misoprostol. Patients are further instructed to return in 14 days for a follow-up, which could include a surgical abortion in the three percent to 7.9% of cases in which the chemical abortion fails.[11]

Many providers, however, deviate from the FDA protocol, extending the RU-486 abortion cut-off to 56 and even 63 days' gestation,[12] cutting the dose of Mifeprex by two-thirds, and handing the patient misoprostol pills to insert vaginally at home two days later.[13] Failure rates at these gestational ages are approximately 17% and 23% respectively.

In the decade preceding FDA approval of RU-486 for use in the United States, advocates of RU-486 promoted the drug as a private, easy, safe and effective method of pregnancy termination,[14] offering women the choice of ending pregnancy at an earlier stage and in a less "invasive," instrumented manner, when compared to surgical and suction abortion methods.[15] In sum, the public was told that access to RU-486 had everything to do with women's privacy and choices.

Cited as justification for RU-486 approval and use were the following goals: "defusing the abortion conflict,"[16] putting abortion "into the medical mainstream and out of this ghettoized place it's been in,"[17] making "abortion … more socially acceptable,"[18] "expanding the number

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[11] See Mifeprex Label ("Medical abortion failures should be managed with surgical termination." Also, "Each patient must understand…that medical abortion treatment failures are managed by surgical termination.") at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited October 10, 2006).

[12] Some abortion providers (e.g., Planned Parenthood of New York City at www.ppnyc.org/services/factsheets/mifep.htm, Capital Care Women's Center at www.capitalcarewomenscenter.com/services.php, and Camelback Family Planning at www.camelbackfamilyplanning.com/abortionpill.html.), even advertise the availability of RU-486 through 63 days LMP, by which time the rate of incomplete abortion, infection, and other complications rises sharply. In U.S. clinical trials, the failure rate for RU-486 abortions jumps to 17% at 50-56 days LMP, and to 23% at 57-63 days LMP, from 8% at 49 days or less. Irving Spitz *et al*., "Early pregnancy termination with mifepristone and misoprostol in the United States," *New England Journal of Medicine* 1998, 338:1241-47.

[13] Evidence of this method deviation can be found in many Adverse Event Reports, including those reporting on the deaths of four California women from toxic shock related to *C. Sordellii.*

[14] Lawrence Lader. RU486: The Pill that Could End the Abortion Wars and Why American Women Don't Have It. Reading, Mass.: Addison-Wesley Publ. Co., 1991, 17-26.

[15] Planned Parenthood of New York City Press Release, December 4, 2000: "Women will now have access to this option of a very safe, early abortion without undergoing an invasive procedure. … By allowing women to take part in their own care, mifepristone offers women more privacy in their decisions and control over their bodies."

[16] Margaret Talbot, "The Little White Pill," *New York Times Magazine*, July 11, 1999, quoting Seattle abortion provider Suzanne Poppema, M.D.

[17] *Ibid*, quoting Carole Joffe, professor of sociology, University of California-Davis.

[18] *Ibid*.

of abortion providers"[19] and even advancing the U.S. aim of "population control"[20] in the developing world. One vocal advocate explained: "Abortion in the U.S. is this degraded, shameful, violence-surrounded thing. …It's not like that in Europe. So that makes our context for medical [e.g., RU-486] abortion unique."[21] Safety and efficacy questions were brushed aside with assurances that several hundred thousand women in France and China had already used RU-486 to induce abortion.[22]

One might reasonably wonder why, when the surgical option is readily available and exponentially safer,[23] the FDA would approve, or the abortion industry would support, a chemical procedure that subjects women to increased pain and risk. To answer this question, it is helpful to understand abortion industry fears concerning the dwindling number of providers, and to assess the industry's leverage and access within the FDA.

The National Abortion Federation reported in May 2004 that the "number of abortion providers has declined by 37% since 1982."[24] In 1997, 36% of ob/gyns reported ever performing elective abortions.[25] Among them, 57% were fifty years of age or older and another 30% were 40 or older.[26] In other words, the abortion industry perceived that—unless drastic measures were taken—it was in danger of losing nearly 57% of its doctors by 2012 and 87% of its doctors by 2022, significantly reducing the availability of abortion in the United States.[27]

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[19] Margaret Talbot, "The Little White Pill," *New York Times Magazine*, July 11, 1999, quoting Seattle abortion provider Suzanne Poppema, M.D.

[20] Nathanson, Bernard, "Drugs for the Production of Abortion: A Review," Obstet & Gyn Survey 25:8; 727-731 (1970); Renate Klein *et al*., RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 59: "It is a further misconception to believe that this [RU-486] research took place in order to expand or improve women's 'choices' to control their reproduction. Quite unmistakenly, the concept evolved as a means of population control. More than 20 years ago, the Center of Population Research of the U.S. National Institutes of Health became interested in the corpus luteum and called for research to determine whether to find 'means to inhibit corpus luteum function is a desirable goal'. The specific intention of such research was to restrict population growth in countries that were judged to be 'under-developed.' If successful, the method(s) could be extended to groups in the United States, Black, Hispanic and Native American Women (Department of Health, Education and Welfare, NIH, USA, 1969)."

[21] Margaret Talbot, "The Little White Pill," *New York Times Magazine*, July 11, 1999, quoting Carole Joffe, professor of sociology, University of California-Davis.

[22] Lawrence Lader. A Private Matter: RU-486 and the Abortion Crisis. Amherst, N.Y.: Prometheus Books, 1995, 115-117.

[23] The Alan Guttmacher Institute, an affiliate of Planned Parenthood, reports that the mortality rate for women who procure a surgical abortion is 0.1 in 100,000 during the first eight weeks of pregnancy, the period for which RU-486 is available for women. Dr. Michael Green, based on usage rates of 460,000 and 4 deaths, suggested that the risk of death from chemical abortion is ten times greater. *See,* Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353;22 *at* 2318.

[24] Abortion Access Project, Fact Sheet: The Shortage of Abortion Providers, May 6, 2004, available at www.abortionaccess.org/AAP/publica_resources/fact_sheets/shortage_provider.htm (last visited October 10, 2006).

[25] Kaiser Family Foundation, *Abortion*, Issue update, Menlo Park, CA: Kaiser Family Foundation, May 1999.

[26] *Ibid.*

[27] Lawrence B. Finer and Stanley K. Henshaw, "Abortion Incidence and Services In the United States in 2000," Perspectives on Sexual and Reproductive Health, 2003, 35(1):6-15.

The industry, then, out of concern for its own preservation, pinned its hopes on chemical abortion. A Kaiser Family Foundation survey, for example, noted: "Many reproductive health groups in the U.S. have looked to widespread availability and marketing of mifepristone … to expand access to abortion in this country."[28] Pediatrician Eric Schaff, who oversaw at least one RU-486 trial, put the matter somewhat more crudely. Objecting to an FDA proposal (never formally adopted) that any doctor dispensing RU-486 would have to be trained in surgical abortion, Dr. Schaff explained, "The whole idea of [RU-486] was to increase access. … [The FDA proposal] kills the drug if it can't be used by primary care providers."[29]

Despite the problems associated with RU-486 (discussed in depth in Section III, below), it looked like a panacea for the abortion industry. Advocates predicted that the number of providers would increase. The Kaiser Family Foundation stated that one-third of all ob/gyns who did not perform abortions said they would be "very" or "somewhat" likely to prescribe mifepristone for abortions if approved by the FDA.[30] Furthermore, rather than limiting abortion procedures to medical doctors alone, advocates saw an opportunity for nurse practitioners, nurses, and others to administer abortions to women.[31]

In June 1989, one year after its introduction into the French market, the FDA issued an import alert on RU-486. The concern was that women would obtain the drug themselves and use it without support from a physician. The wisdom of this policy is supported by the fact that, as the RU-486 label states, nearly *all* users of RU-486 will experience adverse events.[32] But it wasn't long before Democrats, led by then-Representative Ron Wyden of Oregon, seized this opportunity to politicize the approval process.

Under the auspices of the Committee on Small Business's Subcommittee on Regulation, Business Opportunities and Energy, as early as September 18, 1990, Representative Wyden was investigating the FDA's import alert on RU-486, alleging that the FDA's overriding concerns for the alert were political, rather than medical, and that the actions of the FDA were preventing cures for several diseases, including breast and brain cancer, Cushing's disease, glaucoma and

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[28] Kaiser Family Foundation, News Release, June 8, 2000, available at www.kff.org/womenshealth/20000613a-PressRelease2.cfm (last visited October 10, 2006).

[29] Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," *New York Times*, June 8, 2000.

[30] Kaiser Family Foundation, News Release, June 8, 2000, available at www.kff.org/womenshealth/20000613a-PressRelease2.cfm (last visited October 10, 2006).

[31] Press release, Ibis Reproductive Health, the National Abortion Federation, and the Abortion Access Project, May 9, 2006, available at www.prochoice.org/news/releases/20060509.html (last visited October 10, 2006).

[32] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006): "Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction."

diabetes. Two hearings in his committee followed, one in November of 1990[33] and another in December, 1991.[34]

Following these hearings, Representative Wyden introduced legislation to prohibit the FDA from taking any action to bar the import of RU-486 unless the FDA finds that it is being imported for an illegal use.[35]

It is interesting to contrast the interests of Representative Wyden and the abortion industry with the concerns of the American Medical Association (AMA), which offered this view about the health and safety of women who might obtain and use RU-486 without a physician's supervision:

> "[I]t is the AMA's understanding that RU-486 poses a severe risk to patients unless the drug is administered as part of a complete treatment plan under the supervision of a physician…Rumors exist that the FDA, due to political pressure, is standing in the way of research on RU-486. We do not believe this to be true. On the contrary, it is the FDA's responsibility to ban a drug that has not met legal and regulatory requirements for importation into the United States. Because RU-486 has not met these requirements, the FDA complied with its charge and acted well within its authority in issuing its June 9, 1989, automatic detention import alert concerning the drug."[36]

In the meantime, women's groups orchestrated an offensive consisting of media stunts to exert political pressure on the FDA. Lawrence Lader, founding chairman of the then-National Abortion Rights Action League (NARAL), and Ms. Leona Benton, who volunteered to serve as a "test case," traveled to Europe to acquire RU-486 with the specific purpose of being apprehended by Customs agents when they returned on July 1, 1992.[37] Agents seized the pills, and 45 members of the press showed up to publicize her "plight."

Ms. Benton immediately filed suit against the FDA in federal district court (Brooklyn), and Judge Charles Sifton ruled in her favor on July 14. Before she could physically recover the confiscated pills, however, government attorneys filed an appeal with the U.S. Court of Appeals for the Second Circuit, where a three-judge panel reversed Judge Sifton's order. The U.S. Supreme Court accepted an expedited appeal and, on July 17, ruled 7-2 against releasing the

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[33] *RU-486: The Import Ban and its Effect on Medical Research: Hearing before the House Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business*, 101st Cong. (Nov. 19, 1990).

[34] *Safety and Effectiveness of the Abortifacient RU-486 in Foreign Markets: Opportunities and Obstacles to U.S. Commercialization: Hearing before the House Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business*, 101st Cong. (Dec. 5, 1991).

[35] H.R. 875 "RU-486 Regulatory Fairness Act of 1991," introduced February 6, 1991.

[36] *RU-486: The Import Ban and its Effect on Medical Research: Hearing before the House Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business*, 101st Cong. (Nov. 19, 1990) (statement of Dr. John P. Seward, Board Member, American Medical Association).

[37] Lawrence Lader, A Private Matter: RU 486 and the Abortion Crisis. Amherst, N.Y.: Prometheus Books, 1995, 135-136.

pills.[38] In the interim, she and Lawrence Lader gained widespread publicity concerning RU-486 in the media. She had a surgical abortion.[39]

In that same month, Public Media Video released a documentary financed by the Chicago abortion advocacy group, Women's Issues Network, entitled, "Science Held Hostage: RU-486 and the Politics of Abortion," hosted by Cybil Shepard. They held a screening on Capitol Hill.

In the six years since approval, mounting evidence points unavoidably to one conclusion: the political motivations for bringing RU-486 to the U.S. market overwhelmed considerations of women's health and safety.

In a September 28, 2000 interview following the announcement of the FDA's approval of RU-486, then-FDA Commissioner Dr. Jane E. Henney stated: "Politics had no role in this decision."[40] That assurance has been called into question by documents made public this year which reveal the Clinton Administration's vigorous role from 1993 forward[41] in facilitating the abortion drug's entry and approval. The actors behind these documents approached approval as a matter of logistics rather than as involving an open-minded scientific inquiry. One memorandum goes so far as to advise the Administration on how to contextualize the anticipated FDA approval of the drug in terms of "promoting women's health and maintaining the close relationship of the Administration to these [pro-choice women's] groups."[42]

However, had the FDA undertaken a thorough review of the scientific literature evaluating RU-486/prostaglandin abortions before approving RU-486, the agency would have been alerted to paramount safety concerns. Certainly, the FDA Medical Officer's Review, discussed in detail below, falls short of endorsing the safety of RU-486. Even so, only two additional studies are referenced in the Medical Officer's Review[43] apart from discussion of the U.S. clinical trials and the two so-called "pivotal French trials" conducted by the manufacturer. In light of this omission, and more significantly, in light of the FDA's approval of RU-486, one wonders why numerous studies demonstrating the inherent risks to women who undergo RU-486 abortions did not appear to influence the FDA's decision to approve RU-486.

And, in fact, such a thorough review of medical and scientific literature on RU-486 had already been published in 1991 by three women who describe themselves as pro-choice

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[38] *Benten v. Kessler*, 505 U.S. 1084 (1992).

[39] *Ibid*., at 139.

[40] Gina Kolata, "U.S. Approves Abortion Pill; Drug Offers More Privacy, and Could Reshape Debate," *The New York Times*, September 29, 2000.

[41] See, various documents compiled by Judicial Watch, Inc.. and appended to "A Judicial Watch Special Report: The Clinton RU-486 Files," April 26, 2006, available at http://JudicialWatch.org/archive/2006/jw-ru486-report.pdf.

[42] HHS Chief of Staff Kevin Thurm, Memorandum to White House Director of Public Policy Carol Rasco, Subject: RU-486, dated May 11, 1994.

[43] Beverly Winikoff *et al*., "The Acceptability of Medical Abortion In China, Cuba and India," *Int Fam Plan Perspect*. (1997) 23:73-78 & 89; and J.T. Jensen *et al*., "Outcomes of Suction Curettage and Mifepristone Abortion in the United States," *Contraception* (1999): 153-159.

feminists. A brief synopsis of some of the studies they review will help set the context for the discussion of the FDA's approval process, which follows in Part II (below).

Renate Klein,[44] Janice G. Raymond[45] and Dr. Lynette J. Dumble[46] co-authored a "comprehensive literature review and analysis of hundreds of medical and scientific articles on RU 486/PG [prostaglandin], a large percentage of which have a connection with Roussel Uclaf,"[47] the pharmaceutical company that developed RU-486 in the 1980s.

The first clinical trial of RU-486 in humans took place in October 1981 in Geneva, Switzerland after only 17 months of animal research with rats, rabbits and monkeys,[48] although the results of animal trials were not such a resounding success that they justified the rush to human trials. "RU 486 caused the death in two out of three monkeys in toxicity tests,"[49] for example. None of the eleven women in Geneva who were given 200 mg of RU-486 per day for three consecutive days died, but only nine pregnancies were terminated (eight after five days and the ninth at nine days). Furthermore, one woman claimed initially as a "success" later required uterine evacuation, and another woman needed emergency surgery and a blood transfusion due to heavy bleeding.[50] Klein *et al.* describe how the Parisian newspaper *Liberation* reported on the Geneva trial: "Liberation commented that, given these associated complications and risks, RU 486 was no 'abortion miracle.' *Liberation* also reported that RU 486 is not only an anti-progesterone but an anti-glucocorticosteroid which can take the place of cortisone in the adrenal glands, and that contraindications emanating from this double action of the drug could be a problem,"[51] as it turned out to be for two out of three monkeys.

Roussel Uclaf staff proceeded next to clinical trials on small groups of women in France, Sweden, Australia, Holland, the United States of America, England, Finland and China. The manufacturer supplied RU-486 for these trials, and its staff and consultants co-authored articles reporting on the results.[52] The success rates (defined as "a complete termination of pregnancy

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[44] Ms. Klein is a biologist, professor of sociology and women's studies and author/editor of numerous books on reproductive technologies.

[45] Then Professor, University of Massachusetts and associate director of MIT's Institute on Women and Technology.

[46] Then visiting professor of surgery at the University of Texas and senior research fellow in the University of Melbourne's Department of Surgery, Royal Melbourne Hospital.

[47] Renate Klein *et al*., RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 4.,.

[48] *Ibid*., at 9-10.

[49] Lawrence Lader. RU486: The Pill that Could End the Abortion Wars and Why American Women Don't Have It. Reading, Mass.: Addison-Wesley Publ. Co., 1991, 17-26, at 48.

[50] Renate Klein *et al*., RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 10, citing Etienne-Emile Baulieu, "RU-486 as an Antiprogesterone Steroid: From Receptor to Contragestion and Beyond," *Journal of the American Medical Assn*. 262:13; 1808-1814 (October 6, 1989)..

[51] *Ibid*., at 10.

[52] *Ibid*.

without the need for further medical intervention") using RU-486 alone ranged from 54%[53] and 61%[54] to a high of 85%[55] and 90%[56] -- at best substantially below the 99% success rate for surgical abortion.

The Kovacs *et al*. trial, finding a 61% average efficacy, illustrates some of the risks encountered in RU-486 use. A total of 37 women "with amenorrhea of 42 days or less" were given RU-486 twice daily for four days at several different levels of dosage. All patients attended three follow-up visits at one, two and five-to-six weeks after the "therapy" began. In three patients (8%) pregnancy was unaffected by the drug. Two patients required blood transfusion and curettage due to heavy bleeding, and another was found at the second follow-up visit to have an extra-uterine pregnancy. Kovacs *et al*. concluded that "treatment with RU 486 may provide a novel therapy for 'menstrual regulation' but the efficacy of the treatment needs to be improved to compete with alternatives such as vacuum aspiration."[57]

In 1984, researchers in Sweden began using a prostaglandin in conjunction with RU-486 to improve efficacy rates (achieving complete abortions in 32 of 34 women subjects, or 94%), without, however, having first undertaken basic research into the potential adverse effects arising from interactions between these drugs.[58]

In late 1988, the French Minister of Health issued approval for the marketing of RU-486 in France.[59] A distinguished committee of scientific and medical experts, which included the president of France's National Academy of Medicine, the head of Nephrology Department, Necker Hospital (Paris), research directors at the (French) National Institute for Health and Medical Research and National Center for Scientific Research, began reviewing data on 30,000 women who by then had used RU-486. In April 1990, this committee issued its scathing "Report of the International Inquiry Commission on RU 486", which faults the approval of RU-486 on several grounds and which warns of the inherent and well-documented risks of RU-

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[53] Herrmann, W.L., Wyss, Rolf, Riondel, A., Philibert, Daniel, Teutsch, Georges, Sakiz, Eduoard and Baulieu, Etienne-Emile. (1982). Effet d'un stéroide antiprogesterone chez la femme: interruption du cycle menstruel et de la grossesse au début. *C R Acad Sci Paris* 294.933-938.[The effect of an anti-progesterone steroid on women: interruption of the menstrual cycle and early pregnancy. Reports of Proceedings of the Academy of Sciences, Paris].

[54] Kovacs, L., Sas, M., Resch, B.A, Ugocsai, G. Swahn, Marja-Lisa, Bygdeman, Marc and Rowe, PJ. (1984). Termination of early pregnancy by RU 486 - an antiprogestational compound. *Contracep* 29.399-410.

[55] Couzinet, Béatrice, Le Strat, Nelly, Ulmann, André, Baulieu, Etienne-Emile and Schaison, Gilbert. (1986). Termination of early pregnancy by the progesterone antagonist RU 486 (Mifepristone). *New England Journal of Medicine* 315.1565-1570.

[56] Grimes, David A., Mishell, Daniel R., Shoupe, Donna and Lacarra, Maria. (1988). Early abortion with a single dose of the antiprogestin RU-486. *American Journal of Obstetrics and Gynecology* 158: 1307-1312.

[57] Kovacs, L., Sas, M., Resch, B.A, Ugocsai, G. Swahn, Marja-Lisa, Bygdeman, Marc and Rowe, PJ. (1984). Termination of early pregnancy by RU 486 - an antiprogestational compound. *Contracep* 29.399-410.

[58] Bygdeman, Marc and Swahn, Marja-Liisa. (1985). Progesterone receptor blockage: Effect on uterine contractility and early pregnancy. *Contraception* 32; 45-51, cited in Klein *et al*., RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 11.

[59] Report of the International Inquiry Commission on RU 486, April 1990, available at http://www.trdd.org/RU486/RUCIEE.HTM (last visited Oct. 18, 2006).

486/prostaglandin abortions. They note cardiovascular and respiratory risks – a full year before the first such fatality, but already evident from the report of one woman who lapsed into a 36-hour-long coma during an RU-486 abortion.[60]

Among the many serious issues raised by the International Inquiry Commission on RU 486 are these:

- the "very strong anti-glucocorticoid" effect of RU-486 (with which the FDA is now familiar, following the deaths from septic shock of four California women)
- the continued uncertainty surrounding RU-486's mode of action
- the necessity of using a prostaglandin to achieve marginally acceptable effectiveness, in light of the known serious side effects of prostaglandin
- metrorrhagia in over 90% of cases, lasting from 1 to 35 days (in "many cases an emergency 'Revision Uterine' [uterine evacuation] was necessary to contain the hemorrhaging. In certain cases, the only recourse was an emergency blood transfusion, with all the risks this involves.")
- "Beyond far heavier risks [compared to] the surgical method … there is – with the medicinal method – an uncertainty about the result during 5 to 12 days," as well as
  - "failure for 5% of the women who will therefore undergo surgery,
  - "around 5 to 10% persistent hemorrhages will need medicinal or surgical treatment,
  - "absolute necessity, some days after abortion, to [perform] an ultrasound examination and a HCG dosage, to be completely sure there [are] no traces of the fetus."
- the risks to women who do not return for follow-up treatment
- recently published studies demonstrating "a strong stimulating effect by RU 486 on the growth of a breast cancerous cellular line"[61] and immune system inhibition.[62]

On immune system inhibition, one wonders how the FDA could have failed to take note of the World Health Organization's 1991 study,[63] in which "9 of the 341 women (2.6%) with complete abortion and … 5 of the 17 subjects (29.4%) with incomplete abortion" had to be given "antibiotic therapy to prevent or cure suspected genitourinary infection" during the six-week follow-up period.[64] Nearly *thirty percent* of incomplete abortions involved infection.

A last example of facts the FDA should have taken into account in the agency's review of RU-486 is the personal story of Tamara Keta Hodgson, a nurse who took part in the RU-486

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[60] *Ibid*.

[61] The referenced report cites RT Bowden, JR Hissom, MR Moore. (1989) "Growth stimulation of T47D human breast cancer cells by the anti-progestin RU-486," *Endocrinology* 124; 2642-2644.

[62] BJ Van Voorhis, DJ Anderson, and JA Hill (1989), "The effects of RU 486 on immune function and steroid-induced immunosuppression in vitro," *J Clin Endocrinol Metab* 69:1195-1199.

[63] World Health Organization. (1991) "Pregnancy termination with mifepristone and gemeprost: a multicenter comparison between repeated doses and a single dose of mifepristone. *Fertil Steril* 56: 32-40.

[64] *Id*., at 37.

trials conducted by Dr. David Grimes in Los Angeles. In a letter published in the *Los Angeles Times* under the heading "Pros and Cons of 'Dr. Grimes' bitter pill,' " Ms. Hodgson writes:

> I took RU-486 in December, 1986, when I was three weeks pregnant. Twenty-four hours later I began to have severe cramping and started vomiting. When this had gone on for 10 to 12 hours, a friend took me to the County-USC Emergency Room. After an excruciating pelvic exam, I was given a shot of Demerol, which did nothing, and a prescription for a prostaglandin inhibitor to slow down the process, which did relieve the pain. I had mild bleeding for a few days and then six days after taking the drug, I began to hemorrhage. I continued to bleed or spot until mid-March, 1987.
>
> I'm not sure why I had such an extreme response. I chose to take the drug rather than have a surgical abortion because it had been presented to me as a relatively benign experience. I also thought it might help advance the causes of both science and women.
>
> Do I think RU-486 should be licensed in the United States? I'm not sure. I had access to many resources not available to the general population of women who might take this drug. I am a registered nurse who works at one of the most sophisticated hospitals in the world. I was cared for by the research team investigating the drug. I had no children who needed to be cared for.
>
> The same cannot be said for women of the Third World. It also cannot be said for women in the United States who do not have access to adequate health care.[65]

Despite all this, what many abortion advocates promoted as a "miracle pill"[66] has turned out to be anything but. Even before its approval, the medical community knew what American women would soon learn by experience:

- mifepristone interferes with the body's immune response[67]

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[65] *Los Angeles Times*, May 6, 1990, at E-20.

[66] David Van Biema, "But Will It End the Abortion Debate?" *Time*, June 14, 1993; available at http://www.time.com/time/magazine/article/0,9171,978680,00.html (last visited October 20, 2006).

[67] *See,* Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in…mifepristone…enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486."). *See also,* Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors…results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The combined loss of a closed cervix and the protective cervical mucus plug permits contamination of

- it is more inconvenient than surgical abortion[68]
- it is more painful[69]
- it is less effective[70]
- it is associated with more adverse events[71]
- it causes more frequent and more severe hemorrhage than its surgical counterpart[72]

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the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

See also, Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.").

[68] *See* FDA Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006):

> This method of pregnancy termination is of limited value because of the relatively short window of opportunity, [sic] in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.
>
> Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility [sic] including at least a four hours [sic] stay after the administration of the misoprostol.
>
> In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects)...
>
> [In a comparison of medical termination of pregnancy with surgical termination,] [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion…[and] increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients… On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients…

[69] *See, e.g.,* B. Elul, et.al, *Side Effects of Mifepristone-Misoprostol Abortion Versus Surgical Abortion*, *Data From a Trial in China, Cuba, and India*, Contraception 59:107-114, 111 (1999): China—60.3% chemical, 36.0% surgical patients experienced pain / cramps; Cuba—89.2 % chemical, 65.4% surgical; India—61.9% chemical, 36.8% surgical.

[70] *See, e.g.,* Beverly Winikoff, et. al., *Safety, efficacy and acceptability of medical abortion in China, Cuba, and India: A comparative trial of Mifepristone-misoprostol versus surgical abortion*, Am. J. Obstet. Gynecol. 431, 434 (Feb. 1997). Failure Rates: China—chemical 8.6%, surgical .4%; Cuba—chemical 16.0%, surgical 4.0%; India—chemical 5.2%, surgical 0%.

[71] *See, e.g.,* E. Cabezas, *Medical versus surgical abortion,* 63 Internat. J Gynecol. & Obstet. Supp. 1, S141, S144 (1999). Cramping: chemical 60.0%, surgical 48.3%; Nausea: chemical 30.6%, surgical 8.9%; Vomiting: chemical 15.1%, surgical 2.0%.

[72] *See Ibid.*, chemical abortion patients experienced 2.3 days of heavy bleeding, 4.8 days of normal bleeding, and 4.9 days of light bleeding compared to 0.3, 1.8, and 3.3 days for surgical, respectively. Furthermore, 50.8% of chemical abortion patients bled more than expected, compared to 7.3% for surgical patients; and 64.1% of chemical abortion patients bled longer than expected, compared to 18.7% of surgical abortion patients. *See also,* Y.F. Chan, et.al.,

The safety issues associated with RU-486 are discussed in depth in Section III, below.

III. RU-486 APPROVAL IRREGULARITIES

Since FDA approved RU-486 in September 2000, a number of criticisms have been lodged against FDA alleging procedural irregularities in the approval process.[73] The Subcommittee investigators were aware of these criticisms and requested information from FDA regarding the issues raised by opponents of the approval. This section assesses the claims made and FDA's responses to the following allegations: 1) that FDA's approval was based solely on data from uncontrolled trials; 2) that FDA used Subpart H unlawfully when it approved the drug and, furthermore, that the clinical data used in support of the application was insufficient to satisfy Subpart H requirements; and, 3) that FDA unlawfully mandated the unapproved use of a drug, misoprostol, as part of the RU-486 abortion regimen.

A. The Approval was Unlawfully Based Solely on Data from Uncontrolled Trials

FDA's reputation as the world's foremost regulator of drug products is based largely on the rigor which it demands for data submitted in support of drug applications. The law requires, in Section 505(d)(5) of the Food, Drug and Cosmetic Act, that FDA shall not approve a drug when "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[74] "Substantial evidence" means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . . ."[75]

Over the years, FDA's high standard in supervising the production of clinical trial data has been referred to as its "gold standard." Typically, FDA requires data from two clinical trials that are randomized, blinded and controlled against a "comparator" – often a placebo but more typically an alternative therapy.[76] FDA's Section 314.126(e) indicates that "[u]ncontrolled

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Blood Loss in Termination of Early Pregnancy by Vacuum Aspiration and by Combination of Mifepristone and Gemeprost, Contraception 47:85-95, 90 (1993): Groups receiving 200mg, 400mg, and 600mg of mifepristone experienced an average loss of 84.1ml, 99.9ml, and 101.4ml of blood respectively (ranges were 16.8 - 371.3ml, 16.7 - 524.3ml, and 20.8 - 472.4ml, respectively) compared to an average blood loss of 53.2ml for patients undergoing a vacuum aspiration abortion (range of 29.3ml - 226.0ml).

[73] For example several groups have filed a "citizen petition" with FDA regarding RU-486's approval. *See* Citizen Petition of the American Association of Pro Life Obstetricians and Gynecologists, the Christian Medical Association, and Concerned Women for America, Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days' Gestation, Docket No. 02P-0377 (filed Aug. 20, 2002) ("Mifeprex Citizen Petition"). On October 10, 2003, these groups filed a response to the Danco Laboratories and the Population Council's Opposition to the Citizen Petition which was filed in March 2003. These documents are available in FDA Docket No. 02P-0377.

[74] 21 U.S.C. § 355(d)(5).

[75] 21 U.S.C. § 355(d).

[76] FDA issued a guidance document in 1998 ("Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," May 1998)("FDA Clinical Evidence Guidance") that outlines the

studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness."[77] The question of whether the RU-486 trial data was produced solely by uncontrolled clinical trials was examined by the Subcommittee investigators.

The French and American trial data were generated by trials in which the participants were given mifepristone and misoprostol to chemically end pregnancies. The RU-486 regimen was judged to have been effective, "defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure."[78] The studies measured the rate at which RU-486/misoprostol abortions succeeded or failed at different gestational ages.

However, neither the French nor American RU-486 trials randomized trial participants concurrently against either a placebo or the most similar RU-486 alternative, first-trimester surgical abortion.[79] Neither the French trials,[80] nor the American trial was concurrently controlled.[81] Furthermore, no discussion of controls can be found in FDA analyses of the French trials[82] or in the Spitz Study[83] that reported the results of the U.S. trial. Thus, the question arose as to whether the RU-486 trials were in fact uncontrolled.

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requirements of its drug trial policies with respect to proving effectiveness. Additionally, FDA has signed on to the principles enunciated in documents produced by the International Conference on Harmonization on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH").

[77] 21 C.F.R. § 314.126(e).

[78] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

[79] Blinding would have been very difficult to achieve with respect to the medical personnel performing the surgical abortion or dispensing the drugs to the patient, but blinding of abortion evaluators might have been achievable. In any event, scientifically rigorous randomized and concurrently controlled trials could have been performed with limited or no blinding.

[80] Center for Drug Evaluation and Research, Food and Drug Administration, Statistical Review and Evaluation for NDA 2-687 (Mifepristone), at 2-4 (May 21, 1996). The French trial is referred to as FFR/91/486/14. Available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf.

[81] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17, 2006) (on file with Subcommittee).

[82] Center for Drug Evaluation and Research, Food and Drug Administration, Statistical Review and Evaluation for NDA 2-687 (Mifepristone) (May 21, 1996). The French trial is referred to as FFR/91/486/14. Available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf.

[83] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

At the Subcommittee's May 17, 2006 hearing, *RU-486: Demonstrating a Low Standard for Women's Health?,* Dr. Woodcock, Deputy Commissioner for Operations for the Food and Drug Administration, asserted in her written testimony for the Subcommittee that "[FDA's] finding of drug effectiveness was based on a comparison to a historical control of the expected rate of continued pregnancy."[84]

In response to a post-hearing Subcommittee question, FDA noted that the historical control, used in the RU-486 clinical trials, comprised of "the well-established data and pool of medical knowledge concerning both the natural course of pregnancy itself, including the well-documented rate of spontaneous abortion or miscarriage (less than 20%), and surgical abortion."[85] We take this to mean that the spontaneous abortion rate and the rate of induced abortion were together subtracted from the expected rate of ongoing pregnancy. It is important, then, to examine the FDA's claim that the French and U.S. trials were historically controlled.

First, FDA's assertion that the French and U.S. trials were historically controlled appears to be a *post hoc* assertion. There is no mention of any control group in the Spitz Study;[86] the word "control" does not appear in the article. Moreover, an FDA statistician reviewing the French trial data asserted that "[i]n the *absence of a concurrent control group* in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy"[87] (emphasis added). The reviewer made no mention of a historical control to which mifepristone would be compared, and it is well known that controls have to be specified *before* trials are performed. The lack of a prior delineation of the controls demonstrates that FDA's claims are not supported by the record.

Second, the U.S. RU-486 trials were conducted with specific groups of persons excluded. The Spitz Study[88] lists those disqualified from participation as follows:

> "Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or known allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more

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[84] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf.

[85] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17, 2006) (on file with Subcommittee).

[86] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

[87] Center for Drug Evaluation and Research, Food and Drug Administration, Statistical Review and Evaluation for NDA 2-687 (Mifepristone) at 7-8 (May 21, 1996). The French trial is referred to as FFR/91/486/14. Available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf.

[88] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

> than 10 cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had in situ intrauterine devices, were breast-feeding, were receiving anticoagulation or long-term glucocorticoid therapy, had adnexal masses, had ectopic pregnancies, or had signs or symptoms suggesting they might abort spontaneously.[89]

Yet when FDA was asked what populations were excluded from its control group, the Subcommittee was told that "[a] historical control group does not include specific individuals, but rather is based on experience historically derived from the adequately documented natural history of the condition."[90] FDA made this additional point: "Thus, historical control populations usually cannot be assessed with respect to certain variables, such as the inclusion or exclusion of specific sub-populations."[91] This answer is methodologically insufficient, and it underscores the conclusion that, regardless of FDA's statement to the contrary, these trials were uncontrolled. The trial and control groups must be matched to each other in almost all possible ways if there is to be a meaningful control. If it was not possible to match the populations with the historical data set, then a concurrent control should have been used.

Finally, FDA allowed the use of uncontrolled trials for medical abortion because it defined the clinical endpoint too restrictively.[92] Neither spontaneous nor medical abortions produce only simple zero or one outcomes – that is, one-dimensional instances of success or failure. Not all abortions, whether spontaneous or medical, pass by themselves. Many require surgical intervention to be completed, or serious complications may ensue. FDA's cramped definition of RU-486 "effectiveness" ignores this.[93] A control should have been used in the RU-486 trial that compared different methods of producing the experimental outcome – first-trimester pregnancy termination – while assessing each method's ability to manage highly predictable, regular complications of medical abortion (*i.e.*, hemorrhage, incomplete abortion). As the International Conference on Harmonization[94] has noted, "non-defined" external controls

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[89] *Ibid*, at 1241-2.

[90] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17, 2006) (on file with Subcommittee).

[91] *Ibid.*

[92] *Ibid.*

[93] *Ibid.* ("In the case of medical abortion, determining the effectivness of the drug is straightforward, because it is relatively easy to determine whether the pregnancy has been terminated. Therefore, it is unnecessary to utilize a randomized clinical trial design.").

[94] FDA, "International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials," *Notice*, 62 Fed. Reg. 66113 (Dec. 17, 1997) (*FDA Guidance (ICH: E8): General Considerations*). The International Conference on Harmonization "is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health." *See* www.ich.org (last visited October 10, 2006).

– those in which "a comparator group [is] based on general medical knowledge of outcome" – are "particularly dangerous" and "such trials are generally considered uncontrolled."[95] Such a characterization pertains in instances like this in which the study's dependent variable (i.e., the termination of pregnancy) has been defined so narrowly as to give the false impression of complete knowledge of a simple medical outcome.

B. FDA's Abuse of Subpart H

RU-486 was approved through an important part of FDA's drug approval rules called "Subpart H."[96] In the Subcommittee's May 17 hearing, Dr. Woodcock told the Subcommittee, "FDA approved the Mifeprex NDA [new drug application] under Subpart H at the sponsor's request because the Agency determined that post-marketing distribution restrictions on the product were necessary to ensure its safe use."[97]

These rules were promulgated by FDA in 1992 as part of an attempt to correct perceived deficiencies in FDA's approval process made apparent by the need to quickly develop drugs for HIV/AIDS patients. However, in order to benefit from the provisions contained in Subpart H (*e.g.*, its restricted distribution provisions in the case of RU-486) certain conditions must be satisfied, and in the RU-486 instance, Subpart H was unlawfully used for its approval.

Inducing Medical Abortion Does Not Qualify for Subpart H

Supbart H can only be applied to drug products "that have been studied for their safety and effectiveness in treating *serious or life-threatening illnesses*…."[98] (emphasis added). FDA was aware of this requirement, and FDA asserted in its approval memo to the Population Council "that the termination of an unwanted pregnancy is a *serious condition* within the scope of Subpart H…."[99] (emphasis added).

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[95] *FDA Guidance (ICH E10): Choice of Control Group* at 5 (§ 1.3.5). Section 2.5.4 adds the following point to this discussion: "An externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable and the disease or condition to be treated has a well-documented, highly predictable course. It is often possible, even in these cases, to use alternative, randomized, concurrently controlled designs."

[96] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).. The Subpart H rules are found at 21 C.F.R. § 314.500ff.

[97] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf. We note that the Mifeprex Citizen Petition references a letter from Sandra Arnold of the Population Council to FDA, dated Sept. 6, 2000, in which she vociferously protests Mifeprex's approval under Subpart H. Mifeprex Citizen Petition at 20 (". . . it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider.").

[98] 21 C.F.R. § 314.500.

[99] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4

Linguistic gymnastics notwithstanding, pregnancy or the termination of pregnancy is not a "serious or life-threatening illness," and therefore does not fall within the defined reach of Subpart H; the term "serious condition" is not found in the Subpart H rule. Subpart H is intended for the treatment of "serious or life-threatening illnesses," not conditions. There are situations in which pregnancies become serious or life-threatening, but the underlying condition is not "serious or life-threatening." Moreover, pregnancy itself is not an illness. There are situations in which serious or life-threatening complications may arise, but these are atypical events.

It is difficult to find a credible counter-argument from FDA or any private party defending the use of Subpart H to approve RU-486. This is not a mere technicality. If the condition being treated did not qualify for Subpart H approval, then the various restrictions that could be imposed pursuant to Subpart H to ensure the safe distribution of the drug would not have been available to the agency.

The FDA imposed several such restrictions on the distribution of Mifeprex.[100] (These restrictions, however, are less rigorous than what was initially proposed prior to approval.[101])

Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
- Has read and understood the prescribing information of Mifeprex
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going

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Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

[100] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000). Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

[101] FDA "Division Director Memo to File" on Mifepristone NDA, September 17, 1996 (on file with the Subcommittee): "The applicant has appropriately proposed that drug distribution be limited to licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and in the performanceof surgical abortion) who will attend educational seminars on the safe use of this regimen." The final restrictions allow for distribution under the supervision of a physician, rather than limiting it to licensed physicians, and do not require educational training on the safe use of the regimen.

pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
- Must record the Mifeprex package serial number in each patient's record

With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:

- Secure manufacturing, receiving, and holding areas for the drug
- Secure shipping procedures, including tamper-proof seals
- Controlled returns procedures
- Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
- Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
- Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

In addition, the Population Council agreed to two post-marketing studies on the effects of RU-486 on women[102] (though earlier reviews considered six post-marketing studies, four of them were dropped when the drug was approved[103]). In the six years since the approval of RU-486, these studies have not been completed.[104]

The RU-486 Trials Did Not Establish a "Substantial Benefit" for Subpart H

In addition to being intended for drug products studied for their safety and effectiveness in treating serious or life-threatening illnesses, Subpart H is intended only for those products that "provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)"[105] FDA's Approval Memo stated that, for RU-486, "….[t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure."[106] The French and American clinical trial data did not satisfy the requirements established in the

[102] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000). Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

[103] Center for Drug Evaluation and Research, Food and Drug Administration, Office Memo to Population Council (documenting the approval action for RU-486) September 28, 2000. Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

[104] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (July 31, 2006) (on file with Subcommittee).

[105] 21 C.F.R. § 314.500.

[106] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000). Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

Subpart H rules for establishing a meaningful therapeutic benefit to patients over existing treatments.

First, RU-486 was not approved for a medical indication intended for only the treatment of patients who were intolerant of surgical abortion. It was approved to treat the general population of women seeking first-trimester abortions. FDA baldly asserted that there was a clinical benefit for chemical abortion, and made no effort to produce statistical evidence of an actual benefit.

Second, surgery is an integral part of the RU-486 abortion process, because a substantial proportion of women require D&C's after beginning the mifepristone regimen. Therefore, women who have RU-486 abortions must be able to tolerate the surgical procedure. This fact alone makes it all the more difficult to accept FDA's bald assertion of a meaningful therapeutic benefit above that presented by surgical abortion. While such a benefit may exist, the law requires FDA to make its judgments based on scientific evidence. Subpart H requires that both safety and effectiveness be established for the Subpart H drug above the existing standard of care. At the very least, FDA should have required the drug sponsor to conduct non-inferiority trials to generate data for the drug application.

Third, even though some women may prefer RU-486 abortions over surgical abortions, that fact does not establish the existence of a therapeutic benefit in and of itself. One can imagine numerous ways of delivering therapies that are more desirable for the patient – for example, pills rather than injection – but FDA must establish this fact statistically.

Fourth, it appears that no concurrently-controlled trials comparing medical and surgical abortion were required by FDA, because the Agency already knew that medical abortion—i.e., abortion by RU-486—is unambiguously inferior to surgical abortion with respect to safety and effectiveness. Prior to the approval of the RU-486 NDA, the FDA medical officer made the following observations about studies that had compared medical and surgical abortion:

> [In a study comparing medical and surgical abortion in India, Cuba, and China (n = 1373)], [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion (8.6% versus 0.4% in China, 16.0% versus 4.0% in Cuba, and 5.2% versus 0% in India)…. Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients….[107]

> [In another non-concurrent study of 377 patients comparing mifepristone to surgical abortion in the U.S patients], [f]our mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine mifepristone

[107] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

> patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the mifepristone group than in the surgical group (35 days versus 8 days). Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients. The mean difference in bleeding days between cohorts was 9.6 days (95% CI, 6.8, 12.4)…. Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients… Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients…. Nausea or vomiting in the follow-up interval was common in the mifepristone group (68.6%), but rare among surgical patients."[108]

Given these comments, it is impossible to conclude that RU-486 medical abortions provide a meaningful therapeutic benefit over surgical abortion. Consequently, FDA's approval of the RU-486 NDA using Subpart H was unjustified and unlawful.

C. The Highly Unusual Placement of Misoprostol on the Mifeprex Label

When FDA approved the Population Council's RU-486 application it also mandated the use of another drug, misoprostol, as part of a two-drug abortion regimen. The use of misoprostol was not only an unapproved or off-label use – it was actually contraindicated at that time.[109] This aspect of the approval highlights another irregular component of FDA's approach to reviewing the RU-486 NDA. Shortly after FDA's approval of mifepristone, Peter Barton Hutt, a former FDA general counsel and noted commenter on food and drug law, told the Wall Street Journal that FDA appeared to have created "an extraordinary precedent", because FDA was "seemingly encouraging a drug's unapproved use."[110] He added that the agency is in an "embarrassing and uncomfortable position."[111]

The Subcommittee's questions to FDA on this matter have produced some information but no clear sense as to what FDA's policy is with respect to placing off-label or contraindicated drug uses on another drug's label.[112]

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[108] *Ibid.*

[109] On April 17, 2002, the misoprostol label was amended to remove "the contraindication and precaution that Cytotec should not be used in women who are pregnant."

[110] Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1.

[111] *Ibid.*

[112] In addition to questioning the FDA on this matter, the Subcommittee has looked for, and failed, to find any FDA Guidance documents on this topic.

Attention is drawn to two problems. First, it is well known that the NDA-holder for misoprostol (Searle) did not want to have its product used or labeled to reflect off-label uses as an abortifacient. [113] Thus, FDA mandated misoprostol's use in this abortion regimen and placed information about Searle's product on the Mifeprex label. Second, the entire edifice of FDA's regulation of drugs rests on the principle that only indications whose effectiveness has been demonstrated with "substantial evidence" may be placed on the label. FDA has procedures by which new indications can be approved using the supplementary new drug applications. No supplementary drug application was ever filed for misoprostol's use as an abortifacient.

In her prepared testimony before the Subcommittee, Dr. Woodcock noted that the FDA was "aware that questions ha[d] been raised about the use of misoprostol, a drug indicated for the prevention of NSAID-induced gastric ulcers, in the medical abortion regimen with mifepristone, without a separate approval and labeling of misoprostol for this use."[114] She then observed that numerous cases existed "where the labeling of one drug recommends its use with a second drug without the approval of the sponsor of the second drug."[115]

This statement is troubling and warrants further investigation. First, Woodcock's use of "recommends" is grossly inaccurate. In the Mifeprex regimen, the use of misoprostol is mandated. A physician might use an off-label variant of the regimen and, therefore, use another prostaglandin, but the Mifeprex label gives very specific directives to use misoprostol. [116] The non-optional nature of the regimen is carried forward into the language of the Patient Agreement Form which states: "I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3)."[117] Second, Subcommittee investigators finds it problematic that FDA can dictate that a drug – under the proprietary control of a firm whose NDA has been approved – can be approved for a use to which it objects.

In a letter to Chairman Souder, FDA provided two examples in which non-approved uses appear on FDA-approved labels. [118] The examples relate to coronary heart disease and metastatic

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[113] See letter from Searle warning against the use of misoprostol in abortion: http://www.fda.gov/medwatch/safety/2000/cytote.htm (last visited October 20, 2006).

[114] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf.

[115] *Ibid*.

[116] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006).

[117] Mifeprex Patient Agreement, Item # 6, available at http://www.fda.gov/cder/drug/infopage/mifepristone/patientAgreement20050719.pdf (last visited October 20, 2006).

[118] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee). *See also*, See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf.

breast cancer, and the relevant labels should be read to understand the comments that follow.[119] Some comments are in order. First, there is no *mandated* use of the second/off-label drug in either example. Second, in the coronary disease case, the drugs were designed and approved to work on aspects of cardiovascular system-blood pressure regulation. There is nothing unusual in this use of drugs intended to manage cardiac failure.

These facts provide a qualitative difference with the Mifeprex regimen in which misoprostol was *not* designed to work to produce abortions – or uterine contractions for that matter. Rather, misoprostol was a medication intended to protect the gastro-intestinal tract from adverse events related to the use of non-steroidal anti-inflammatory medication – an indication far removed from misoprostol's novel application as an abortifacient.

Finally, FDA's Herceptin/Taxol example is somewhat disingenuous. After reading each drug's label, one recognizes that Taxol is approved for metastatic breast cancer treatment as a single agent, and so is Herceptin, but neither is specifically indicated for metastatic breast cancer treatment where no prior chemotherapy has been given. The combination use is approved (but not MANDATED) for patients with metastatic breast cancer overexpressing HER2 protein who have not received any prior chemotherapy.

Both drugs are approved for use in metastatic breast cancer. Herceptin's indication is more specifically tied to use when there is overexpression of HER2 protein. If there has been no other chemotherapy given then both may be used together. FDA seems to be splitting hairs when it claims that the use of Taxol in such cases is off-label. That characterization depends upon a fine distinction having to do with a specific tumor marker and whether or not other chemotherapy had been used.

The tenuousness of FDA's examples leads the Subcommittee to conclude that FDA is having difficulty finding examples that parallel the mandated, dissimilar off-label use of misoprostol in the Mifeprex regimen.

IV. SAFETY

Since the introduction of RU-486 to the U.S. market, the FDA has acknowledged, as of May 2, 2006, the deaths of six women associated with the drug, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection.[120] These and other cases have added up to a total of 1070 adverse event reports (AERs) as of April 2006.[121]

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[119] The relevant information can be found using the website: <www.rxlist.com>.

[120] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[121] Numbers do not convey the full story. More telling are the first-hand accounts of women who have lived these events. Below are some examples from the Individual Safety Reports (ISRs) which describe in detail the type of experience RU-486 chemical abortion has turned out to be (mistakes are as they appear in the originals):

Event of January 1, 2000, reported September 27, 2000, one day before the approval of Mifeprex: "I was issued RU-486 in effort of obtaining an abortion. I followed directions exactly, and after taking the ru-486, I was in

excrutiating physical pain, for at least 12 hours straight and I was bleeding extremely excessively. I was bleeding through my pants but was in so much pain I couldn't even clean myself. It was the worst physical pain I've ever experienced in my life. This extreme pain was constant the whole 12 hours, it did not let up at all the whole time. I vomited continuously but couldn't even hold my head up. I had unbelievable abdominal pains, I can't even put in words. I couldn't speak, eat, drink, sit up, and had difficulty breathing. The only thing I could do was lie on the floor and pull my hair to deal with the pain. I couldn't clean myself or go to the bathroom, I thought I was going to die. After about 7 hours of this, I really wanted to die because I couldn't take the pain anymore. I wanted to call the hospital but I was hours from any hospital because I went to our cabin in a remote area to have privacy during this time. The administering clinic was closed since it was the weekend…. I was not informed of the extent of these side effects, I was told it would be just like a menstrual period. I never would have taken this had I been properly informed, even of the possibility of those effects…I was not told that this drug was experimental and not approved by the FDA…I believe they outright lied to me…when I returned to the clinic after the abortion was complete, they were not very attentive or interested in me, I explained to them my pains even though they didn't ask me any questions. I filled out a questionairre that they gave me before I took the drug and they said I have to do the questionnaire ever couple hours during the abortion, but when I offered it to them upon return, they didn't even want the questionaire, they didn't take it."

Event of July 26, 2002, reported September 28, 2002: "28 year old Gr5. Para 2 Ab 2 at 6 weeks 5 days gestation received 200 mg Mifeprex on [redacted] and inserted 800 mcg misoprostol vaginally on [redacted] at 11:00 a.m. The bleeding was 'normal' until 3:30 p.m. when it became heavier. That evening she stated 'it was like water coming out of me' and she felt dizzy. That evening she reported that she briefly 'passed out' twice. She went to an emergency room and received [missing] litres of IV fluid and had a D&C. Her hemoglobin on arrival was 8.7 gm/dl and was [missing] gm/dl after the D&C. She was started on iron supplementation. On [redacted] her hematocrit was 28% at the clinic and she reported that she was resting, on limited to light activity and doing well."

Event of August 15, 2004, reported July 25, 2005: "I took RU-486 last year and it caused me serious problems. After 15 days after taking it I hemorrhaged while at work requiring subsequent D&C, then had an infection that would not go away despite multiple antibiotics. I ended up being hospitalized and having multiple tests due to the infection and pain. I was hospitalized for four days in september of last year. Even after being hospitalized I was very ill for quite some time. I believe it took me until December to fully recover, during this time I lost quiet a bit of weight and had to enter counseling as a result of all the problems after using RU486."

Event of October 31, 2002, reported August 13, 2005: "Previous to 2002 I had two pregnancies and two live births…In 2002, 2003, and 2004, I had a three abortions at a very early stage, using the 'French' pill—RU-486—with each being almost exactly a year apart. I had the same experience each time. I developed a very bad case of bacterial vaginosis…I also was told to insert the final pill vaginally in all three cases. I had no idea it could even be taken orally."

Event of September 8, 2004, reported August 17, 2005: "I was given 2-step Abortion Pill. In the middle of the night I was awoken by severe abdominal pains. Having had endometriosis has built my pain tolerance quite high, but this pain was excruciating. Between the pain and diarrhea, I wanted to pass-out. I laid on the cold tile of the bathroom floor for 4 hours to keep me from fainting and because I couldn't get up. I thought it would eventually taper off, but after 4 hours I was exhausted and couldn't tolerate the pain. I yelled until my sister woke up to help me and asked her to call 911. She knew that I never go to the hospital, much less ask for 911, she immediately called. At the hospital, blood tests –b-hcg- kept coming back positive and I was still in alot of pain. They sent me for ultrasounds, blood tests again, and pelvic exams. I asked for more morphine, but they told my sister that they gave me the maximum dose and were surprised that I was still moaning of pain. The doctor said that my body was going through labor over and over, but wasn't ridding of anything. After the 3rd pelvic exam and blood test, the HCG count started coming down."

Event of December 14, 2005, reported December 27, 2005: "Approximately 2 1/2 weeks after taking Mifeprex and Cytotec to end a pregnancy, I began having very heavy bleeding. This was after I had not bled for a week, and after a 2 week follow up at a clinic—in which was told I was fine—I began hemorraging on the evening of the 14th, passing clots approximately 3 inches in size. I went through approximately 7 pads in 2 hours. The clinic wanted me to wait until the morning to get care from their facility, but when we called the local ER, they told me I needed to come in right away to get examined. I was cold, weak, and fatigued during the 2 hours my bleeding was excessively heavy. Unfortunately I was not able to make it into the ER because I am a single mother of 4, and had noone to care

A. Adverse Events for RU-486

These reports are based on the FDA's Adverse Event Reporting System (AERS), a voluntary system, with inherent underreporting. Common estimates of the proportion of adverse events actually captured by FDA in AERS are from one to ten percent. FDA acknowledges that it does not capture all adverse events associated with a drug: "When evaluating reports from the AERS system, it is important to recognize several caveats. First, *accumulated case reports cannot be used to calculate actual incidences of adverse events or estimates of risk for a product, as the reporting of adverse events is a voluntary process with inherent underreporting*"[122] (emphasis added).

The Government Accountability Office (GAO) has also commented on the underreporting of Adverse Events: "FDA cannot establish the true frequency of adverse events in the population with AERS data. The inability to calculate the true frequency makes it hard to establish the magnitude of a safety problem, and it makes comparisons of risks across similar drugs difficult."[123]

FDA nonetheless claims that it is capturing most adverse events associated with RU-486: "Because healthcare professionals who prescribe Mifeprex have agreed in writing" (with the manufacturer, Danco, *not* the FDA) "to report 'any hospitalizations, transfusions or other serious events' to the manufacturer, FDA believes that there are unlikely to be significant numbers of serious adverse events, including deaths, associated with Mifeprex that have not been reported to the Agency."[124]

During the Subcommittee staff's review of the 1070 Adverse Event Reports that had been reported through April 2006, ISRs were found that had been submitted through MedWatch, the voluntary reporting mechanism for AERS, rather than through Danco. FDA acknowledged that these reports were not matched by reports submitted through Danco,[125] undermining the Agency's claim that it is capturing most adverse events.

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for my children. Luckily for me, the bleeding lessened. I was told it was 'normal' to bleed for up to 4 weeks, but I am NOW at day 32 and still bleeding."

[122] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[123] Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process GAO-06-402 March 31, 2006.

[124] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (July 31, 2006) (on file with Subcommittee).

[125] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (June 30, 2006) (on file with Subcommittee).

In light of FDA's repeated claim that it captures most RU-486-related adverse events—despite the Agency's own acknowledgement of underreporting and experience to the contrary—it is important to note that there is no true enforcement mechanism, either by Danco or the FDA, for ensuring that doctors report all adverse events, and there is little incentive on the part of the prescribing physician to do so.[126]

Even Danco has noted that the FDA's "obligatory" reporting system is of little value. In 2003, Dr. Richard Hausknecht, Medical Director for Danco, wrote that "[t]he obligatory reporting of adverse events is limited to transfusions, hospitalizations, ongoing pregnancies or 'other serious adverse events,' which allows considerable subjective judgment on the part of the providers. In addition, the reporting of other common adverse events may not be reported at all."[127]

Moreover, emergency room personnel and medical professionals who do not prescribe RU-486, but who may likely treat the infected or hemorrhaging patient, or provide surgical intervention, *have no obligation whatsoever to report adverse events for RU-486*, even assuming that the healthcare worker is aware the patient took the RU-486 drug regimen.[128] In such scenarios, prescribing physicians may remain unaware of adverse events that take place after they administer RU-486, alleviating them of reporting requirements. This underscores the fact that there is not an accurate picture of the total adverse events that are being experienced with this drug.

In addition to the fact that there is no accurate number of adverse events to serve as a realistic "numerator" for evaluating the rate of adverse events actually being experienced in the population, the FDA does not use an accurate figure for the true number of patients who have taken RU-486 as a "denominator." Rather, FDA accepts and reports "estimates" proposed by Danco. The most recent estimate is that 612,000 women in the U.S. have used RU-486 as of July 24, 2006.[129]

This estimate is likely inflated, since Danco arrives at its estimate by basing it on the number of packages sold (in three-pill packages of 200 mg pills) and multiplying that number by three to account for the number of doses that are given at the off-label 200 mg dose (rather than

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[126] Although RU-486 is approved for use through 49 days of pregnancy, it is commonly prescribed in the United States up to 63 days of pregnancy. Physicians also commonly prescribe a dosing regimen that is different from that approved by the FDA. Therefore, it has been suggested that in fact there is a *dis*incentive on the part of prescribing physicians to report adverse events that may be attributed to a physician's negligence or willingness to prescribe a regimen that is outside the FDA-approved regimen for RU-486.

[127] Hausknecht, R., "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," *Contraception* 67 (2003) 463-465.

[128] Treating personnel might never know that a woman has taken RU-486; Women who seek medical treatment for adverse reactions after RU-486 may be too sick to disclose, may fail to disclose, or may simply refuse to disclose (because she does not want it in her medical record) that she has taken the RU-486 drug regimen.

[129] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17. 2006) (on file with Subcommittee).

the FDA approved 600 mg dose).[130] That Danco is allowed to provide a loosely-figured *estimate* flouts the restricted approval provision for RU-486, which requires Danco to distribute the drug with a tracking system allowing the company to track packages "to the patient level while maintaining patient confidentiality."[131]

For FDA to rely upon guesses as a basis for understanding safety problems with RU-486 is highly problematic. Danco's estimate is used as the denominator for determining the rate of adverse events associated with the drug. The larger the denominator, the lower the percentage of adverse events. This inaccuracy of using Danco's estimate is inexcusable in light of the way the estimate is relied upon to determine and discuss the rate of adverse events associated with RU-486.

B. RU-486 Safety Issues Known Prior to Approval

Prior to FDA's approval of RU-486, the Agency's own medical experts recognized that any benefits that could be gained from the use of this drug for a "medical abortion" were limited at best and that significant dangers were inherent in its use. These dangers are especially acute when compared to surgical abortion. According to the FDA's medical reviewer, writing before the drug's approval:

> This method of pregnancy termination is of limited value because of the relatively short window of opportunity, [sic] in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.
>
> Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility [sic] including at least a four hours [sic] stay after the administration of the misoprostol.
>
> In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects)...
>
> [In a comparison of medical termination of pregnancy with surgical termination,] [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical

[130] Richard Hausknecht, Medical Director for Danco, described how Danco estimates the usage figures for RU-486: "Denominators… were estimated from sales figures. Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg), …[an] estimated range was based upon Planned Parenthood practices and National Abortion Federation (NAF) polling of their membership practices…[and by] [a]djusting for utilization patterns of providers." *Contraception* 67 (2003): 463-65.

[131] CDER Office Memo to Population Council, September 28, 2006. At http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited September 28, 2006).

> abortion…[and] increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients… On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients….[132]

The negative physical experience of RU-486 was explained this way by Dr. Tom Tvedten, an abortion provider in Little Rock, Arkansas: "With medical termination, the discomfort is significant because they have to go through mini-labor…There's a lot of hard cramps and usually significant bleeding. It's cheaper, safer and less painful to have a surgical termination."[133]

In fact, as explained in the RU-486 label, "nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction,"[134] including: abdominal pain; uterine cramping; nausea; headache; vomiting; diarrhea; dizziness; fatigue; back pain; uterine hemorrhage; fever; viral infections; vaginitis; rigors (chills/shaking); dyspepsia; insomnia; asthenia; leg pain; anxiety; anemia; leucorrhea; sinusitis; syncope; endrometritis / salpingitis / pelvic inflammatory disease; decrease in hemoglobin greater than 2 g/dL; pelvic pain; and fainting.[135]

The FDA's Medical Officer's review notes that, "[m]ore than one adverse event was reported for most patients…Approximately 23% of the adverse events in each gestational age group were judged to be severe."[136]

In addition to these known, startling adverse effects, of which the FDA was aware during the RU-486 NDA review process, the incredibly high failure rate of the drug was also known, averaging 14.6% in the U.S. trial testing the drug through 63 days gestation.

The FDA's Medical Officer's review noted that in the U.S. trial of 2015 women, "[a] total of 295 patients were classified as having failed medical abortion."[137] This represents a

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[132] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

[133] John Leland, *Under Din of Abortion Debate, an Experience Shared Quietly*, N.Y. TIMES, Sept. 18, 2005, *at* http://www.nytimes.com/glogin?URI=http://www.nytimes.com/2005/09/18/national/18abortion.html&OQ=_rQ3D1&OP=41647c1fQ2FQ2AQ7EklQ2AbBG)ABB7FQ2AFqqjQ2AqQ2FQ2A42Q2A-_7VB-_YQ2A42_lBA7VB-vC7KY. (Quoting Dr. Tom Tvedten of Little Rock, Arkansas).

[134] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006).

[135] *Ibid.*

[136] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

[137] *Ibid.*

failure in 14.6% of total patients. "Of these patients, 79 (27%) had ongoing pregnancies, 126 (43%) had incomplete abortions, 30 (10%) requested and had surgical terminations, and the remaining 60 (20%) patients had surgical terminations performed because of medical indications directly related to the medical procedure."[138]

The "best" outcome was in the patient group consisting of women whose pregnancies were less than or equal to 49 days. In this group, 7.9% of patients required surgical intervention after taking RU-486. As the gestational age increases, the failure rate of RU-486 increases rapidly, to 17% in the 50-56 days gestation group, and 23% in the 57-63 days gestation group.

By any objective standard, a failure rate approaching eight percent and requiring subsequent surgical intervention as the "best" outcome is a dismal result. Nonetheless, the Medical Officer stated that "[t]he 92% success rate in the ≤ 49 days group is an acceptable one."[139] This failure rate, along with the anticipated adverse events that patients would experience, is explicit in the FDA Medical Officer's review, and also part of the RU-486 label.[140]

Despite these known problems with adverse events and high failure rates, the FDA recommended and gave approval for distributing this drug to women.

B. Post-Approval Hemorrhage, Infections and Deaths

As stated above, the FDA has acknowledged the deaths of six U.S. women associated with RU-486, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions and 88 cases of infection.[141] A quarter all the patients were hospitalized.[142] These and other cases add up to a total of 1070 adverse event reports (AERs) as of April 2006.

A review[143] of only a portion of all the reported AERs demonstrates in real world experience how women have suffered after taking dangerous drug. Out of only 607 unique adverse events submitted to the FDA, the high number of serious and life-threatening events is startling:

> The most frequent [adverse event reports] were hemorrhage (n=237) and infection (66). Hemorrhages included 1 fatal, 42 life threatening, and 168 serious case; 68 required transfusions. Infections included 7 cases of septic shock (3 fatal, 4 life-threatening) and

[138] *Ibid.*

[139] *Ibid.*

[140] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006).

[141] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[142] *Ibid.*

[143] M. M. Gary, D. J. Harrison, *Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient*, The Annals of Pharmacotherapy, February 2006, 40.

> 43 cases requiring parenteral antibiotics. Surgical interventions were required in 513 cases (235 emergent, 278 nonemergent). Emergent cases included 17 ectopic pregnancies (11 ruptured). Second trimester viability was documented in 22 cases (9 lost to follow-up, 13 documented fetal outcome). Of the 13 documented cases, 9 were terminated without comment on fetal morphology, 1 was enrolled in fetal registry, and 3 fetuses were diagnosed with serious malformations, suggesting a malformation rate of 23%.[144]

Since this review by Gary and Harrison, there have been hundreds more adverse event reports and two additional reported septic infection deaths. Nearly all among the afflicted and dead who experienced these serious adverse events following RU-486 were healthy women of child-bearing age. (This is in sharp contrast to other drugs with inherent risks—Viagra, for example—which result in adverse events often after repeated use over long intervals of time, in patients with other risk factors associated with age or disease.) Without access to emergency room services, women who suffered severe hemorrhage would have died.

In total, there are eight known deaths following RU-486: four Californians and one Canadian from *C. Sordellii* septic infection; a Tennessee woman with ruptured ectopic pregnancy; a Swedish teen, from massive hemorrhage; and a British female, from "unknown etiology," (but her clinical presentation of shock and an autopsy revealing one liter of blood in her stomach makes sepsis a plausible etiology).[145]

Five of the eight known deaths following the use of RU-486 have been the result of a toxic shock-like syndrome initiated by the bacteria *C. Sordellii.* This bacteria is thought to exist in low numbers in the reproductive tracts of many women and is normally contained by the immune system.[146] Experts in immunology,[147] pharmacology[148] and maternal-fetal medicine[149]

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[144] *Ibid*.

[145] *Ibid*.

[146] Letter to the Editor, James A. McGregor and Ozlem Equiles, *Risks of Mifepristone Abortion in Context*, Contraception 2005, 71: 161.

[147] *See,* Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in…mifepristone…enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486.")

[148] *See,* Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors…results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The combined loss of a closed cervix and the protective cervical mucus plug permits contamination of the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

have suggested that because RU-486 interferes with the immune response, the bacteria, if present, are then able to flourish, causing a widespread, multi-organ infection in the woman.

The infections are *not* accompanied by a fever, and symptoms match those that are expected after taking the RU-486 regimen (cramping, pain, bleeding, nausea, vomiting), making detection of the fast-spreading infection difficult. Each of the women infected with *C. Sordellii* after RU-486 were dead within five to seven days.

The FDA describes the clinical presentation of *C. Sordellii* infection the following way:

- Rapid onset of influenza like symptoms (nausea, vomiting, and weakness)
- Hypothermia or *absence* of fever
- *Absence* of purulent discharge
- Localized pelvic tenderness may be *absent*
- Elevated hematocrit and marked leukemoid reaction
- Progressive refractory hypotension
- Marked edema with peritoneal and pleural effusions
- Rapidly fatal despite aggressive treatment[150] (emphasis added).

To investigate the nature of the *C. Sordellii* bacteria, the FDA and CDC held the "Emerging Clostridial Disease" workshop on May 11, 2006.[151] Workshop presenters – experts in the fields of pharmacology, immunology, and maternal-fetal medicine – noted that the rapid growth of the *C. Sordellii* bacteria likely forecloses effective treatment;[152] that there is no currently identifiable "window of opportunity" for treatment once a woman is infected, even with major interventions such as hysterectomy;[153] and that antibiotic prophylaxis was unlikely to provide any protection in the RU-486 / *C. Sordellii* context.[154] The fatality rate has been 100% for the women who contracted *C. Sordellii* infection after RU-486.

In an effort to dismiss any association between RU-486 and the *C. Sordellii* deaths, some have promoted the idea that *C. Sordellii* is linked to pregnancy and childbirth, not the abortion pill. However, in five years, five women have died from this infection after taking RU-486. In contrast, the FDA has noted that there were "only five additional cases not associated with

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[149] *See,* Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.").

[150] Food and Drug Administration "Center Director Briefing" June 27, 2005 (on file with the Subcommittee).

[151] A full transcript for the meeting is available at: http://www.fda.gov/cder/meeting/clostridial/transcript.pdf (last visited October 13, 2006).

[152] Letter to the Editor, James A. McGregor and Ozlem Equiles, *Risks of Mifepristone Abortion in Context*, Contraception 2005, 71: 161.

[153] Public Workshop on Emerging Clostridial Disease," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Transcript available at http://www.fda.gov/cder/meeting/clostridial/transcript.pdf (last visited October 13, 2006).

[154] *Ibid.*

mifepristone/misoprostol retrieved with a text search of the entire AERS database"[155] of 3.5 million records.[156]

Distinguishing the 100% fatality rate with this infection following RU-486 among women who were otherwise healthy, the FDA noted, "[t]he patients in these 5 [non-RU-486 related] cases had weakened or altered immune function due to chemotherapy and age (neonatal & elderly patients), and use of multiple antibiotics. None of these five cases involved intravaginal product administration and 3 cases had a fatal outcome. *In contrast to these 5 additional cases in [3.5 million] AERS, the 4 U.S. confirmed cases of Clostridium Sordellii infection with medical abortion involved healthy patients and all cases had fatal outcome*"[157] (emphasis added).

A more extensive database search for any reported *C. Sordellii* infections since 1925 found a total of eleven fatal cases related to post-partum/ob-gyn infection or to spontaneous abortion.[158] In contrast with this small number of cases (11 since 1925) five women in five years are known to have died from *C. Sordellii* following RU-486.

Experts studying the immune suppression properties of RU-486 have found that it has the ability to block innate immune response.[159] Lazar had published information as early as 1992

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[155] Memorandum, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, April 12, 2006, From [redacted], Division of Drug Risk Evaluation, Through: [redacted] Division of Drug Risk Evaluation, TO: [redacted] Division of Reproductive and Urologic Products. Subject: Supplementary investigations related to reports of fatal infections associated with mifepristone and misoprostol use for medical abortion. [handwritten note: DFS 4/17/06 Consult #3]

[156] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[157] Memorandum, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, April 12, 2006, From [redacted], Division of Drug Risk Evaluation, Through: [redacted] Division of Drug Risk Evaluation, TO: [redacted] Division of Reproductive and Urologic Products. Subject: Supplementary investigations related to reports of fatal infections associated with mifepristone and misoprostol use for medical abortion. [handwritten note: DFS 4/17/06 Consult #3]

[158] Dennis L. Stevens, M.D., PhD., *Clostridium sordellii: Clinical Settings, Diagnostic Clues and Pathogenic Mechanisms*, Public Workshop on Emerging Clostridial Disease," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Available at http://www.fda.gov/cder/meeting/clostridial/stevens.pdf (last visited October 13, 2006).

[159] *See,* Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in…mifepristone…enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486."). *See also,* Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors…results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The

about the increase in fatal septic infection in mice after receiving RU-486, which caused the survival rate to drop dramatically from the control level of 71% to only 15%.[160] Nonetheless, the theory that RU-486 suppresses the immune system was only noted by the FDA as late as 2003,[161] and it wasn't until 2004 that the Agency conducted the minimal inquiry of a literature review to examine the immune suppression properties of RU-486:.

> "The Division of Anti-Infective Drug Products (DAIDP) reviewed the medical literature to examine the potential impact that either or both mifepristone and misoprostol might have on human immune function. They concluded, 'Systemic levels of mifepristone and misoprostol may both influence the host response to infection via their anti-inflammatory effects, respectively. In theory, *these effects may predispose an individual to infection or may predispose an infected individual to a worse outcome*. Such roles are apparently dependent on dose, timing, and rates of uptake and intracellular degradation in different target tissues'"[162] (emphasis added).

Beyond this, there is little more in the thousands of pages of documents provided to the Subcommittee to indicate an extensive FDA examination of the immune suppression properties of RU-486.

In the meantime, women who take RU-486 are exposing themselves to an exponentially greater risk of infection or death as compared to the alternative of surgical abortion. The risk of death from infection is at least ten times greater than surgical abortion during the first eight weeks of pregnancy.[163] In addition to *C. Sordellii* infection, women taking RU-486 have developed other infections following the abortion pill regimen. The FDA has acknowledged 88 reported cases of infection following RU-486.

The most frequent serious adverse event is hemorrhage, where women who lost enough blood as to require transfusions. These cases of massive hemorrhage comprise 12% of the RU-

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> combined loss of a closed cervix and the protective cervical mucus plug permits contamination of the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

See also, Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.").

[160] G. Lazar, *et al.*, *Modification of septic shock in mice by the antiglucocorticoid RU 38486*, 36 Circulatory Shock 180 (1992).

[161] FDA Division of Anti-Infective Drug Products, Report of Medical Officer Consultation (Intravaginal Misoprostol), November 19, 2003, at 4 (on file with the Subcommittee)..

[162] FDA Mifeprex plus Misoprostol Postmarketing Safety Review, November 15, 2004, at 24 (on file with the Subcommittee).

[163] *See,* Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353;22 *at* 2318. The mortality rate for women who procure a surgical abortion is 0.1 in 100,000 during the first eight weeks of pregnancy, the period for which RU-486 is available for women. Dr. Michael Green, based on usage rates of 460,000 and 4 deaths, suggested that the risk of death from chemical abortion is ten times greater. The rate could be higher, if an accurate numerator is used for the true number of patients who have taken RU-486.

486 AERS.[164] A review of the AERS through September 2005 finds that fifteen women suffered hemorrhages so serious that they lost over half of their entire blood volume and would have died without rapid access to emergency room services.[165]

According to Dr. Donna Harrison, who testified before the Subcommittee at the May 17 hearing *RU-486: Demonstrating a Low Standard for Women's Health?*, "In my experience as an ob-gyn, the volume of blood loss seen in the life-threatening cases is comparable to that observed in major surgical trauma cases like motor-vehicle accidents. This volume of blood loss is rarely seen in early surgical abortion without perforation of the uterus, and it is rarely seen in spontaneous abortion."[166]

As with other adverse events associated with RU-486, no risk factors for hemorrhage have been identified. Rather, they are unpredictable and sporadic.[167]

The proven health risks and demonstrated association with fatal septic infections necessarily prompt urgent consideration of this drug's immediate withdrawal from the market.

V. RECOMMENDATIONS

The high incidence of adverse events has prompted Danco, in cooperation with the FDA, to take steps to alert women and the medical community to the dangers of the drug:[168]

- "Dear Health Care Provider" Letter, April 19, 2002 (warning of danger of ruptured ectopic pregnancies).[169]
- "Dear Emergency Room Director" Letter, November 12, 2004 (warning of infection, heavy bleeding and ruptured ectopic pregnancy).[170]
- "Dear Health Care Professional" Letter, November 12, 2004 (warning of infection, heavy bleeding and ruptured ectopic pregnancy).[171]
- Updated label, December 22, 2004 (reflecting danger of infection, heavy bleeding and ruptured ectopic pregnancy).[172]

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[164] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[165] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Donna Harrison, M.D.) Available at http://reform.house.gov/UploadedFiles/Harrison%20Testimony%20-%20scan%20test.%20w%20attchmts.pdf.

[166] *Ibid.*

[167] *Ibid.*

[168] See Danco's website, http://www.earlyoptionpill.com/.

[169] Available at http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf (last visited October 14, 2006).

[170] Available at http://www.fda.gov/cder/drug/infopage/mifepristone/DearER.pdf (last visited October 14, 2006).

[171] Available at http://www.fda.gov/cder/drug/infopage/mifepristone/DearHCP.pdf (last visited October 14, 2006).

- "Dear Health Care Provider" Letter, July 19, 2005 (warning of the cases of fatal septic shock).[173]
- Updated label, July 19, 2005 (warning of danger of fatal *C. Sordellii* infections).[174]

In light of the significant health risks posed by this drug, the current restrictions, and the letters and label changes subsequent to approval are demonstrably insufficient to protect women from the dangers of RU-486. Rather, the FDA possesses the authority to suspend or withdraw approval of the drug under various provisions. The most important, and perhaps necessary and justified for removing RU-486 from the market, is the Imminent Hazard authority possessed by the Secretary of Health and Human Services.

"Imminent Hazard" is defined and the criteria to be considered are set forth in 21 CFR 2.5:

> (a) Within the meaning of the Federal Food, Drug and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists.
>
> (b) In exercising his judgment on whether an imminent hazard exists, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury.

Under this provision, the Secretary's decision is subject to judicial review, but the courts are deferential to the Secretary's conclusions.[175] Within the context of RU-486, the unpredictability and frequency of serious adverse event and death (discussed in Section III above) warrants withdrawal of this dangerous drug from the market.

The FDA also possesses the authority to unilaterally withdraw approval of a drug under 21 CFR 314.530. RU-486 falls into the withdrawal categories of this provision:

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[172] Available at http://www.fda.gov/cder/foi/label/2004/020687lbl_Revised.pdf (last visited October 14, 2006).

[173] Available at http://www.fda.gov/medwatch/safety/2005/mifeprex_deardoc_071905.pdf (last visited October 14, 2006).

[174] Available at http://www.fda.gov/cder/drug/infopage/mifepristone/DearHCP.pdf (last visited October 14, 2006).

[175] See *Forsham v. Califano*, 442 F. Supp. 203 (D. D.C. 1977)(this case appears to be the only instance in which the "imminent hazard" authority of the HHS Secretary has invoked). See also *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of O. Carter Snead, Assoc. Professor, University of Notre Dame Law School). Available at http://reform.house.gov/UploadedFiles/Snead%20Testimony.pdf.

(a)(1) A post-marketing clinical study fails to verify clinical benefit

Since its approval, RU-486 has been associated with six known U.S. deaths of healthy women.[176] The safety problems associated with RU-486 are discussed above. Additionally, because women who visit the emergency room arrive with symptoms virtually identical to those associated with miscarriage,[177] deaths within the U.S. following the use of RU-486 may be higher, but unreported.

Moreover, as discussed above, the mortality rate for surgical abortion for the first eight weeks of pregnancy is 0.1 per 100,000.[178] The makers of RU-486 report that 575,000 women have used the drug (based on units shipped, not units prescribed, and based on the assumption that one tablet—rather than the FDA-approved three—is administered to the patient;[179] the actual number of women who have taken the drug may be much lower). Using the figure of 575,000 women having taken RU-486, this works out to a known death rate of approximately 1.39 per 100,000, nearly *14 times* greater than surgical abortion. As noted above, Subpart H drug approval is conditioned on "meaningful therapeutic benefit." The statistics demonstrate that medical abortion is far more dangerous than the existing treatment of surgical abortion, which is proof of a lack of clinical benefit.

(a)(3) Use after marketing demonstrates that post-marketing restrictions are inadequate to assure safe use of the drug product

Experience shows that post-marketing restrictions on RU-486 are inadequate to assure the safe use of the product, because the medical community has ignored them on a widespread basis. As noted earlier in this report, abortion providers routinely use RU-486 beyond the time periods approved by the FDA[180] and with dosing regimens that stray from the FDA's approved

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[176] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, (May 2, 2006) (on file with Subcommittee).

[177] "Dear Emergency Room Director" Letter from Danco Laboratories to emergency room directors, (Nov. 12, 2004), *at* http://www.fda.gov/cder/drug/infopage/mifepristone/DearER.pdf.

[178] Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353:22 *at* 2318.

[179] *Ibid.*

[180] Some abortion providers (e.g., Planned Parenthood of New York City at www.ppnyc.org/services/factsheets/mifep.htm, Capital Care Women's Center at www.capitalcarewomenscenter.com/services.php, and Camelback Family Planning at www.camelbackfamilyplanning.com/abortionpill.html.), even advertise the availability of RU-486 through 63 days LMP, by which time the rate of incomplete abortion, infection, and other complications rises sharply. In U.S. clinical trials, the failure rate for RU-486 abortions jumps to 17% at 50-56 days LMP, and to 23% at 57-63 days LMP, from 8% at 49 days or less. Irving Spitz *et al*., "Early pregnancy termination with mifepristone and misoprostol in the United States," *New England Journal of Medicine* 1998, 338:1241-47.

regimen.[181] While off-label use of drugs is common, it runs contrary to the entire purpose of the regulatory regime approved for RU-486 under Subpart H.

The FDA is aware of the medical community's refusal to heed the regulations it instated on RU-486. In its own words, the FDA "is aware that…some [physicians] may have chosen to use a modified version of the Patient Agreement form. However, these decisions are made by physicians exercising their own judgment about what is best for their patients."[182]

This is contrary to the detailed Risk Management Program, explained in the FDA memo detailing the drug's approval, which states: "the signed agreement form will be given to the patient for her reference and another kept in the medical records," and "[the prescribing physician] must provide each patient…with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well."[183] The FDA determined that these restrictions were critical to the safe use of the drug, and in spite of this, physicians have refused to heed them.

(a)(4) The applicant fails to adhere to the post-marketing restrictions agreed upon

Although the FDA stipulated that the manufacturer have systems in place to track the distribution of RU-486 "to the patient level," and that require physicians to "record the Mifeprex package serial number in each patient's record,"[184] Danco has not provided reliable patient numbers, but rather estimates.[185]

In addition to the FDA requiring patients to sign a Patient Agreement form, the Population Council agreed, as part of the approval process, to "auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms." It is unclear whether the Population Council, Danco, or any other entity associated with the production of RU-486 has adhered to this requirement.

(a)(5) The promotional materials are false or misleading

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[181] R. Hausknecht, "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," *Contraception* 67 (2003): 463-65: "Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg)."

[182] Letter from Patrick Ronan, Associate Commissioner for Legislation Department of Health and Human Services FDA to Hon. Mark E. Souder, (March 16, 2006) (on file with Govt. Reform Subcommittee on Criminal Justice, Drug Policy, and Human Resources).

[183] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000) (available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf).

[184] *Ibid.*

[185] Richard Hausknecht, Medical Director for Danco, described how Danco estimates the usage figures for RU-486: "Denominators… were estimated from sales figures. Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg), …[an] estimated range was based upon Planned Parenthood practices and National Abortion Federation (NAF) polling of their membership practices…[and by] [a]djusting for utilization patterns of providers." *Contraception* 67 (2003): 463-65.

The FDA conditioned approval of RU-486 on tracking its use "to the patient level." In spite of this, the manufacturer estimates the usage of its drug for its promotional materials.[186] This affects the perceived safety of the drug, as the manufacturer may be overstating its actual usage in comparison with the adverse events reported.

Both the "Imminent Hazard" provision and the regulatory provision for approval withdrawal under Subpart H provide sufficient authority for the Administration to remove this dangerous drug from the market.

VI. CONCLUSION

The integrity of the FDA in the approval and monitoring of RU-486 has been substandard and necessitates the withdrawal of this dangerous and fatal product before more women suffer the known and anticipated consequences or fatalities. RU-486 is a hazardous drug for women, its unusual approval demonstrates a lower standard of care for women, and its withdrawal from the market is justified and necessary to protect the public's health.

[186] *Ibid*. *See also*, Letter from David W. Boyer, Assistant Commissioner for Legislation, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, (May 2, 2006) (on file with Subcommittee); *FDA Announces Mifeprex Not Cause of One of Two Recent Abortion-Related Deaths*, KAISER NETWORK DAILY REPORTS, (April 11, 2006) *at* http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=36534. ("We stand behind the safety profile of the drug, which has been used by approximately 575,000 women in this country since FDA approval in 2000," quoting Cynthia Summers, director of marketing and public affairs at Danco Laboratories, originally in Wall Street Journal, April 11, 2006.)

(Slip Opinion)

Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortions

Section 1461 of title 18 of the U.S. Code does not prohibit the mailing of certain drugs that can be used to perform abortions where the sender lacks the intent that the recipient of the drugs will use them unlawfully. Because there are manifold ways in which recipients in every state may lawfully use such drugs, including to produce an abortion, the mere mailing of such drugs to a particular jurisdiction is an insufficient basis for concluding that the sender intends them to be used unlawfully.

December 23, 2022

MEMORANDUM OPINION FOR THE GENERAL COUNSEL
UNITED STATES POSTAL SERVICE

In the wake of the United States Supreme Court's recent decision overruling *Roe v. Wade*, 410 U.S. 113 (1973),[1] you have asked for this Office's view on whether section 1461 of title 18 of the United States Code prohibits the mailing of mifepristone and misoprostol, two prescription drugs that are commonly used to produce abortions,[2] among other purposes. Memorandum for Christopher Schroeder, Assistant Attorney General, Office of Legal Counsel, from Thomas J. Marshall, General Counsel, United States Postal Service, *Re: Request for an Interpretation of 18 U.S.C. § 1461*, at 1 (July 1, 2022) ("USPS Request"). Originally enacted as part of the Comstock Act of 1873, section 1461 currently declares "[e]very article or thing designed, adapted, or intended for producing abortion," as well as "[e]very article, instrument, substance, drug, medicine, or thing which is advertised or described in a manner calculated to lead another to use or apply it for producing abortion," to be "nonmailable matter" that the United States Postal Service ("USPS") may not lawfully deliver. 18 U.S.C. § 1461.

We conclude that section 1461 does not prohibit the mailing, or the delivery or receipt by mail, of mifepristone or misoprostol where the sender

[1] *See Dobbs v. Jackson Women's Health Org.*, 142 S. Ct. 2228 (2022).

[2] *See* Ctrs. for Disease Control & Prevention, U.S. Dep't of Health & Hum. Servs., *Abortion Surveillance—United States, 2019*, 70 MMWR Surveillance Summaries, Nov. 26, 2019, at 8, https://www.cdc.gov/mmwr/volumes/70/ss/ss7009a1.htm.

lacks the intent that the recipient of the drugs will use them unlawfully.[3] This conclusion is based upon a longstanding judicial construction of the Comstock Act, which Congress ratified and USPS itself accepted. Federal law does not prohibit the use of mifepristone and misoprostol. Indeed, the U.S. Food and Drug Administration ("FDA") has determined the use of mifepristone in a regimen with misoprostol to be safe and effective for the medical termination of early pregnancy.[4] Moreover, there are manifold ways in which recipients in every state may use these drugs, including to produce an abortion, without violating state law. Therefore, the mere mailing of such drugs to a particular jurisdiction is an insufficient basis for concluding that the sender intends them to be used unlawfully.[5]

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[3] A cognate provision, 18 U.S.C. § 1462, imposes similar abortion-related prohibitions on using an express company or other common carrier for "carriage" of such items. Our analysis in this memorandum is applicable to that provision as well.

Sections 1461 and 1462 refer not only to persons who transmit such items by mail or by common carrier—the senders—but also to individuals who "knowingly cause[]" such items to be mailed, *id.* § 1461; "knowingly take[]" any such items from the mail for the purpose of circulating or disposing of them, *id.*; or "knowingly take[] or receive[]" such items from an express company or common carrier, *id.* § 1462. In the different contexts of obscenity and child pornography, courts of appeals have held that section 1461 applies to the act of the recipient who orders the nonmailable material and thereby "causes" it to be mailed. *See, e.g.*, *United States v. Carmack*, 910 F.2d 748, 748 (11th Cir. 1990); *United States v. Johnson*, 855 F.2d 299, 305–06 (6th Cir. 1988). *But see Johnson*, 855 F.2d at 307–11 (Merritt, J., dissenting); *United States v. Sidelko*, 248 F. Supp. 813, 815 (M.D. Pa. 1965). As far as we know, however, these provisions have never been applied to prosecute the recipients of abortion- and contraception-related materials. Moreover, the court of appeals decisions we discuss below construed the relevant provisions of the Comstock Act to turn on the nature of the sender's intent, not that of the recipient. Consistent with this practice, we focus on the sender throughout this memorandum. To the extent a recipient might be covered, however, our analysis herein would apply and therefore section 1461 would not prohibit that person from ordering or receiving the drugs if she does not intend that they be used unlawfully.

[4] *See Mifeprex (Mifepristone) Tablets*, U.S. Food & Drug Admin. 2 (Mar. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf (mifepristone label); *see also Mifeprex (Mifepristone) Information*, U.S. Food & Drug Admin., https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/mifeprex-mifepristone-information (last updated Dec. 16, 2021).

[5] For purposes of this opinion, we assume but do not decide that section 1461 could be constitutionally applied to the mailing of drugs intended to produce abortions. We also assume without deciding that state law, as well as federal, is relevant to the application of section 1461. In addition, we do not address here whether and under what circumstances the mailing of mifepristone or misoprostol might violate other federal laws. Finally, as

I.

The Comstock Act has a long and complex history. The original 1873 law was the handiwork of Anthony Comstock—"a prominent anti-vice crusader who believed that anything remotely touching upon sex was . . . obscene"—who successfully lobbied Congress and state legislatures in the nineteenth century to enact expansive laws "to prevent the mails from being used to corrupt the public morals." *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60, 70 n.19 (1983) (omission in original) (quotation marks and citations omitted); *see also* Priscilla J. Smith, *Contraceptive Comstockery: Reasoning from Immorality to Illness in the Twenty-First Century*, 47 Conn. L. Rev. 971, 982–84 (2015). Originally entitled "An Act for the Suppression of Trade in, and Circulation of, obscene Literature and Articles of immoral Use," Act of Mar. 3, 1873, ch. 258, 17 Stat. 598 ("1873 Act"), the Act is perhaps best known for having prohibited the distribution of a wide range of writings until courts and the Executive Branch determined that the Free Speech Clause of the First Amendment significantly limited the permissible reach of the law, *see, e.g.*, *Bolger*, 463 U.S. at 69–75. In addition, the Act also included several restrictions on the conveyance of things designed to prevent conception or to produce abortion.[6] Congress largely repealed the references to contraceptives in

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you note, USPS Request at 3, some states have independently enacted laws to restrict the mailing of these drugs for abortion purposes within their jurisdiction. *See, e.g.*, Tex. Health & Safety Code § 171.063(b-1). We do not here assess the possible effect of federal law on such state restrictions, other than to note our agreement with your view that the doctrine of intergovernmental immunity would preclude application of such state laws against USPS employees who are complying with their duties under federal law. *See Intergovernmental Immunity for the Department of Veterans Affairs and Its Employees When Providing Certain Abortion Services*, 46 Op. O.L.C. __, at *1–5, *10 (Sept. 21, 2022).

[6] The original 1873 Act consisted of five sections, three of which are relevant to this opinion. Section 1 of the Act prohibited, *inter alia*, the sale, distribution, or possession, in the District of Columbia and federal territories, of "any drug or medicine, or any article whatever, for the prevention of conception, or for causing *unlawful* abortion," along with advertisements for contraceptives and abortion services and information about how to obtain them. 1873 Act § 1, 17 Stat. at 598–99 (emphasis added). Congress chose not to include that prohibition when it comprehensively enacted title 18 into positive law in 1948. *See* Pub. L. No. 80-772, § 21, 62 Stat. 683, 864 (1948) (repealing, *inter alia*, 18 U.S.C. § 512 (1946)).

Section 2 of the Act, which eventually became codified as section 1461, criminalized the mailing of, *inter alia*, "obscene, lewd, or lascivious" writings; "any article or thing

1971. *See* Pub. L. No. 91-662, 84 Stat. 1973 (1971) (discussed *infra* Part I.C).

In its current form, section 1461, which is derived from section 2 of the 1873 Act, begins by declaring "[e]very obscene, lewd, lascivious, indecent, filthy or vile article, matter, thing, device, or substance" to be "nonmailable matter" that "shall not be conveyed in the mails or delivered from any post office or by any letter carrier." 18 U.S.C. § 1461. The next clauses declare nonmailable "[e]very article or thing designed, adapted, or intended for producing abortion, or for any indecent or immoral use; and [e]very article, instrument, substance, drug, medicine, or thing which is advertised or described in a manner calculated to lead another to use or apply it for producing abortion, or for any indecent or immoral purpose." *Id.*; *see also* 39 U.S.C. § 3001(a) (likewise declaring such matter to be "nonmailable"). Section 1461 further makes it a felony to "knowingly use[] the mails for the mailing, carriage in the mails, or delivery" of any such things, or to "knowingly cause[]" them "to be delivered by mail according to the direction thereon." 18 U.S.C. § 1461. In addition, 18 U.S.C. § 1462 imposes two other, related prohibitions: it makes it unlawful to bring those same things "into the United States, or any place subject to the jurisdiction thereof," and it prohibits the knowing use of "any

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intended or adapted for any indecent or immoral use or nature"; and "any article or thing designed or intended for the prevention of conception or procuring of abortion." 1873 Act § 2, 17 Stat. at 599. Before Congress enacted title 18 into positive law in 1948, the provision that is now section 1461 was codified at 18 U.S.C. § 334 (1925–1926).

Section 3 of the 1873 Act prohibited all persons "from importing into the United States" any of the "hereinbefore-mentioned articles or things"—referring to the items prohibited by sections 1 and 2. 1873 Act § 3, 17 Stat. at 599. One year later, *see* Act of June 20, 1874, ch. 333, 18 Stat. pt. 3, at 113–14, Congress codified section 3 of the Comstock Act as section 2491 of the Revised Statutes and, in doing so, replaced the section's reference to the "hereinbefore-mentioned articles or things" with a list of articles and things pulled from the other provisions of the Comstock Act, *see* Rev. Stat. § 2491 (1st ed. 1875), 18 Stat. pt. 1, at 460; *see also* Rev. Stat. § 2491 (2d ed. 1878), 18 Stat. pt. 1, at 457. In supplying content to these words, Congress prohibited the importation of articles or things "for causing unlawful abortion," reflecting the language of section 1 of the original Comstock Act. Rev. Stat. § 2491 (1st ed. 1875), 18 Stat. pt. 1, at 460. Congress consistently retained the words "unlawful abortion" in follow-on versions of this restriction, including in subsequent Tariff Acts through 1930, after which the provision was codified at 19 U.S.C. § 1305.

express company or other common carrier or interactive computer service" for "carriage" of such items "in interstate or foreign commerce."[7]

Over the course of the last century, the Judiciary, Congress, and USPS have all settled upon an understanding of the reach of section 1461 and the related provisions of the Comstock Act that is narrower than a literal reading might suggest. This construction occurred long before the Supreme Court's decisions in *Griswold v. Connecticut*, 381 U.S. 479 (1965), and *Roe* and thus was not dependent upon the Court's recognition of constitutional rights regarding the prevention or termination of pregnancy. Beginning early in the twentieth century, federal courts construed the provisions not to prohibit all mailing or other conveyance of items that can be used to prevent or terminate pregnancy. By the middle of the century, the well-established, consensus interpretation was that none of the Comstock Act provisions, including section 1461, prohibits a sender from conveying such items where the sender does not intend that they be used unlawfully. USPS accepted that construction and informed Congress of it. On several occasions, Congress reenacted and amended the Comstock Act against the backdrop of the judicial precedent in a manner that ratified the federal courts' narrowing construction.

A.

Since early in the twentieth century, federal courts have agreed that section 1461 and related Comstock Act provisions do not categorically prohibit the mailing or other conveyance of items designed, adapted, or intended for preventing or terminating pregnancy.

In 1915, in *Bours v. United States*, 229 F. 960 (7th Cir. 1915), the U.S. Court of Appeals for the Seventh Circuit reversed the conviction of a doctor who had mailed a letter addressing how a woman might procure an "operation" from him. The court noted that Congress enacted the provision that is now section 1461 pursuant to its "national power of controlling the mails" and held that, "[i]n applying the national statute to an alleged offensive use of the mails at a named place, it is immaterial what

[7] The importation prohibition—along with 19 U.S.C. § 1305 (prohibiting the importation into the United States of "any drug or medicine or any article whatever for causing unlawful abortion")—derives from section 3 of the original 1873 Act, *see* § 3, 17 Stat. at 599. The common-carrier prohibitions derive from an 1897 law extending the mailing prohibitions of the original Comstock Act to common carriers. *See* Act of Feb. 8, 1897, ch. 172, 29 Stat. 512.

the local statutory definition of abortion is, what acts of abortion are included, or what excluded." *Id.* at 964. The court further held that "[t]hough the letter of the statute would cover all acts of abortion," under a "reasonable construction," the statute should not be read to prohibit the mailing of advertisements for a procedure a doctor would perform in order "to save [the] life" of the woman. *Id.* Because the indictment had not drawn this distinction, the defendant had no opportunity to explain whether he had intended to perform the operation "only under such circumstances as would make it the duty of any reputable physician to perform the act." *Id.* at 965. Therefore, the court reversed the judgment and remanded the case. *Id.* at 966.

Fifteen years later, in *Youngs Rubber Corp. v. C.I. Lee & Co.*, 45 F.2d 103 (2d Cir. 1930), the U.S. Court of Appeals for the Second Circuit also reasoned in dicta that the statute could not be construed as expansively as its language might suggest. *Youngs Rubber* was a trademark infringement suit in which the defendants argued that the plaintiff's business was unlawful because it involved sending Trojan condoms to druggists for retail sale via the mail and common carriage, a practice that—according to the defendant—violated the Comstock Act. *Id.* at 108. "Taken literally," the appeals court wrote, the Comstock Act's "language would seem to forbid the transportation by mail or common carriage of anything 'adapted,' in the sense of being suitable or fitted, for preventing conception or for any indecent or immoral purpose, even though the article might also be capable of legitimate uses and the sender in good faith supposed that it would be used only legitimately." *Id.* "Such a construction," the court cautioned, "would prevent mailing to or by a physician of any drug or mechanical device 'adapted' for contraceptive or abortifacient uses, although the physician desired to use or to prescribe it for proper medical purposes." *Id.* The court observed that New York law did not prohibit supplying such articles to physicians "or by their direction or prescription." *Id.* at 109 (quotation marks omitted). Reasoning that "[t]he intention to prevent a proper medical use of drugs or other articles merely because they are capable of illegal uses is not lightly to be ascribed to Congress," the court construed the statute's contraception and abortion prohibitions to "requir[e] an intent on the part of the sender that the article mailed or shipped by common carrier be used for illegal contraception or abortion." *Id.* at 108.

In 1933, the U.S. Court of Appeals for the Sixth Circuit embraced the same limiting construction of the Comstock Act. *Davis v. United States*,

62 F.2d 473 (6th Cir. 1933), involved a defendant who was convicted of, among other things, the sale of "rubber sundries" to druggists that were delivered by common carrier. *Id.* at 474. Invoking the "rule of reasonable construction," *id*. at 475, the *Davis* court reversed the conviction because the district court did not permit the admission of evidence that the defendant had sent the items intending that they be used for "treatment and prevention of disease" rather than to prevent conception, *id.* at 474. The court quoted with approval *Youngs Rubber*'s view that the statute should be read to "requir[e] an intent on the part of the sender that the article mailed or shipped by common carrier be used for illegal contraception or abortion or for indecent or immoral purposes," *id.*, and noted that the "soundness of its reasoning commends itself to us," *id.* at 475. The court accordingly rejected the district court's conclusion that the statute "brings within the condemnation of each section articles or things that are capable of being used for the specified purposes without respect to their having a legitimate use, and without regard to the intent of the persons mailing [them]," *id.* at 474, holding instead that "intent that the articles . . . shipped in interstate commerce were to be used for condemned purposes is a prerequisite to conviction," *id.* at 475.

Three years later, the Second Circuit revisited the issue and adopted *Youngs Rubber*'s dicta as a holding in *United States v. One Package*, 86 F.2d 737 (2d Cir. 1936). In that case, a New York gynecologist had imported vaginal pessaries from a Japanese sender who had asked the doctor to use them in her practice to assess whether they were useful for contraceptive purposes. *Id.* at 738. At the time, New York law prohibited the sale or provision of articles for the prevention of conception, but it included an exception for the provision of such things to physicians "who may in good faith prescribe their use for the cure or prevention of disease." *Id.* (citing N.Y. Penal Law § 1145 (Consol. Laws, c. 40)). The doctor testified that she prescribed the items only where her patient had a health-related reason such that "it would not be desirable for a patient to undertake a pregnancy," which the court of appeals apparently understood to fall within the exception under New York law that permitted physicians to provide patients with contraceptives for particular purposes. *Id.*[8] The court quoted favorably, and at length, from the dicta in *Youngs Rubber*, and noted the accord of the Sixth Circuit in *Davis*. *Id.* at 738–39. It then

[8] The court of appeals noted that the accuracy and good faith of the doctor's testimony was "not questioned." *One Package*, 86 F.2d at 738.

dismissed the case because none of the relevant provisions should be read to prohibit the mailing or importation of items to prevent or terminate pregnancy with the intent that they be used for lawful purposes. *Id.* at 739–40. The court reasoned that it was appropriate to, in effect, imply the insertion of the adjective "unlawful," which expressly modified the word "abortion" in some provisions of the Comstock Act, to modify the terms "prevention of conception" and "abortion" throughout the various provisions that derived from the Act. *Id.* [9] The court elaborated:

> [W]e are satisfied that this statute, as well as all the acts we have referred to, embraced only such articles as Congress would have denounced as immoral if it had understood all the conditions under which they were to be used. Its design, in our opinion, was not to prevent the importation, sale, or carriage by mail of things which might intelligently be employed by conscientious and competent physicians for the purpose of saving life or promoting the well being of their patients. The word "unlawful" would make this clear as to

[9] The case involved the "prevention of conception" prong of the Tariff Act of 1930—a descendent provision of the original Comstock Act—which prohibited importing articles "for the prevention of conception or for causing *unlawful* abortion." *One Package*, 86 F.2d at 738 (emphasis added) (quoting 19 U.S.C. § 1305(a) (1934)); *see also supra* note 6. The court noted that the original 1873 Comstock Act likewise used the adjective "unlawful" to modify "abortion" in one of its provisions (section 1—involving the sale and possession of abortifacients in federal territories) but not in others, and not as to articles for preventing conception. *One Package*, 86 F.2d at 739. The court reasoned that Congress could not reasonably have had the design to make the "unlawful" nature of the intended use an element of the offense under some of the abortion-related prohibitions but not others, or as to the importation of items used for abortion but not those used for contraception. *See id.* ("[I]n the Comstock Act, . . . the word 'unlawful' was sometimes inserted to qualify the word 'abortion,' and sometimes omitted. It seems hard to suppose that under the second and third sections articles intended for use in procuring abortions were prohibited in all cases while, under the first section, they were only prohibited when intended for use in an 'unlawful abortion.'"). Instead, the court reasoned, the adjective "unlawful" must in effect be read to modify all of the prohibitions. *Id.*; *see also id.* at 740 (Learned Hand, J., concurring) ("[I]t is of considerable importance that the law as to importations should be the same as that as to the mails; we ought not impute differences of intention upon slight distinctions in expression."). The *One Package* court's analysis that the adjective "unlawful" should be read to modify all of the provisions of the Comstock Act is bolstered by the 1874 Congress's understanding of the term "hereinbefore-mentioned articles" in section 3 of the Comstock Act to prohibit the import only of articles, drugs, or medicines "for causing unlawful abortion." *See supra* note 6; Rev. Stat. § 2491 (1st ed. 1875), 18 Stat. pt. 1, at 460.

> articles for producing abortion, and the courts have read an exemption into the act covering such articles even where the word "unlawful" is not used. The same exception should apply to articles for preventing conception. . . . It seems unreasonable to suppose that the national scheme of legislation involves such inconsistencies and requires the complete suppression of articles, the use of which in many cases is advocated by such a weight of authority in the medical world.

Id.

The Second Circuit again reaffirmed this construction of the statute shortly thereafter in *United States v. Nicholas*, 97 F.2d 510 (2d Cir. 1938), which involved the Comstock Act's prohibition on mailing information about contraception. Citing *Youngs Rubber* and *One Package*, the court in *Nicholas* noted: "We have twice decided that contraceptive articles may have lawful uses and that statutes prohibiting them should be read as forbidding them only when unlawfully employed." *Id.* at 512.[10] Applying this reading, the court held that USPS was required to deliver a magazine containing contraception-related information to a magazine editor who might then distribute it to persons such as physicians who could use the information lawfully. *Id.* The court further held that USPS should detain a book containing such information when it was addressed to an individual "about whom nothing" was known "except that he was not a physician," *id.* at 511, but allowed for the recipient to "prove whether he is among the privileged classes" whose possession of the book "would be lawful," *id.* at 512.

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[10] Although *Nicholas* described the relevant inquiry as being whether the articles were "unlawfully employed," rather than whether the sender *intended* that they be used unlawfully—the touchstone the court had adopted in *Youngs Rubber* and *One Package*—this difference in phrasing does not reflect a departure relevant to our analysis. The court's invocation of those two earlier decisions without qualification, as well as its further citation to *Davis*, indicates that it did not intend to deviate from the interpretation of the Act that the court had adopted in those decisions. Both the Historical and Revision Note to section 1461 and subsequent federal decisions understood *Nicholas* similarly. *See* 18 U.S.C. § 1461 (Historical and Revision Note) (observing that *Nicholas* followed "[t]he same rule" as *Davis*, which held that "the *intent* of the person" that a mailing "be used for condemned purposes was necessary for a conviction" (emphasis added)); *United States v. Gentile*, 211 F. Supp. 383, 385 n.5 (D. Md. 1962) (citing, *inter alia*, *Nicholas* for the proposition that "contraceptive devices [must be] shipped and received with intent that they be used for *illegal* contraception or abortion").

In 1944, the U.S. Court of Appeals for the D.C. Circuit also narrowly construed the statute in the context of a report about contraceptive materials that a consumer group had published and mailed to individuals who submitted a signed certificate attesting, "I am married and use prophylactic materials on the advice of a physician." *Consumers Union of United States, Inc. v. Walker*, 145 F.2d 33, 33 (D.C. Cir. 1944). The appeals court explained that it was "inclined to follow the interpretation [of the Comstock Act] which has been adopted in other circuits," citing to *Nicholas*, *Davis*, *Youngs Rubber*, and *One Package*. *Id.* at 35 & n.11. It therefore concluded that "Congress did not intend to exclude from the mails properly prepared information intended for properly qualified people," and held that the report "was proper in character within the meaning of those decisions." *Id.* at 35.

Subsequent judicial discussions of the relevant Comstock Act provisions recognized the narrowing construction upon which the courts of appeals had converged. *See, e.g.*, *United States v. Gentile*, 211 F. Supp. 383, 385 n.5 (D. Md. 1962) ("It seems clear under the authorities that in order to make out an offense under this paragraph the Government should be required to allege and prove that contraceptive devices are shipped and received with intent that they be used for *illegal* contraception or abortion or for indecent or immoral purposes." (citing *Youngs Rubber*, *Davis*, and *Nicholas*)); *United States v. H.L. Blake Co.*, 189 F. Supp. 930, 934–35 (W.D. Ark. 1960) ("It would seem reasonable to give the word 'adapted' a more limited meaning than that above suggested and to construe the whole phrase 'designed, adapted or intended' as requiring an intent on the part of the sender that the article mailed or shipped by common carrier be used for illegal contraception or abortion or for indecent or immoral purposes." (quoting *Youngs Rubber*, 45 F.2d at 108)); *United States v. 31 Photographs*, 156 F. Supp. 350, 357 (S.D.N.Y. 1957) (characterizing the appellate court decisions as "upholding importation of contraceptives and books dealing with contraception when sought to be brought into the country for purposes of scientific and medical research," such that "only contraceptives intended for 'unlawful' use were banned" (citing, *inter alia*, *One Package*, *Nicholas*, *Davis*, and *Walker*)); *see also Poe v. Ullman*, 367 U.S. 497, 546 n.12 (1961) (Harlan, J., dissenting) ("[B]y judicial interpretation . . . the absolute prohibitions of the [Comstock] law were qualified to exclude professional medical use." (citing *Youngs Rubber*, *Davis*, and *One Package*)).

As the court in one of those later cases noted, the analysis in *Youngs Rubber* "has been cited many times and has become the law to be applied to the facts where the question of a violation of the statute . . . is before the court." *H.L. Blake Co.*, 189 F. Supp. at 934. Under that "law to be applied," the court explained, "it is well established that the defendants should not be convicted unless it is established beyond a reasonable doubt that at the time they mailed the sample packages of prophylactics . . . they intended them to 'be used for illegal contraception.'" *Id.* at 935 (quoting *Youngs Rubber*, 45 F.2d at 108).[11]

B.

Congress has amended the Comstock Act's provisions numerous times since the federal courts' decisions in *Bours*, *Youngs Rubber*, *Davis*, *One Package*, *Nicholas*, and *Walker*, each time perpetuating the wording of the Act's abortion-related provisions. Moreover, as we explain in greater detail below, USPS accepted the courts' narrowing construction of the Act in administrative rulings, and it informed Congress of the agency's acceptance of that construction in connection with Congress's amendment of the contraception-related provisions of the Comstock Act.

We conclude that Congress's repeated actions, taken "[a]gainst this background understanding in the legal and regulatory system," *Texas Dep't of Housing & Cmty. Affs. v. Inclusive Cmtys. Project*, 576 U.S. 519, 536 (2015), ratified the Judiciary's settled narrowing construction. *See id.* ("If a word or phrase has been . . . given a uniform interpretation by inferior courts . . . , a later version of that act perpetuating the wording is presumed to carry forward that interpretation." (omissions in original) (quoting Antonin Scalia & Bryan A. Garner, Reading Law: The Interpre-

[11] The leading cases that established this accepted construction—*Youngs Rubber*, *One Package*, and *Davis*—each involved items that could be used to prevent conception rather than to produce abortion. Nevertheless, the canonical passage from *Youngs Rubber*, repeated in each of the cases and in others thereafter, referred both to items designed to prevent conception and to those designed to induce abortions. Moreover, the court in *One Package* went to lengths to explain that all of the relevant Comstock Act prohibitions should be read consistently to require proof of a sender's intent to facilitate unlawful downstream use. *See supra* note 9; *see also Bours*, 229 F. 960 (construing narrowly the prohibition on mailing of information about how to obtain abortions). We therefore agree with your assessment that "there is no apparent reason why the case-law principles applicable to contraceptive articles (formerly) under Section 1461 would not also apply to abortion-inducing articles under the same provision." USPS Request at 3 n.3.

tation of Legal Texts 322 (2012))); *Lorillard v. Pons*, 434 U.S. 575, 580 (1978) ("Congress is presumed to be aware of an administrative or judicial interpretation of a statute and to adopt that interpretation when it reenacts a statute without change."); *cf. Bragdon v. Abbott*, 524 U.S. 624, 645 (1998) ("When administrative and judicial interpretations have settled the meaning of an existing statutory provision, repetition of the same language in a new statute indicates, as a general matter, the intent to incorporate its administrative and judicial interpretations as well."); *Forest Grove Sch. Dist. v. T.A.*, 557 U.S. 230, 244 n.11 (2009) (holding that when Congress amended the Individuals with Disabilities Education Act without altering the text of a provision that the Supreme Court had previously interpreted, Congress "implicitly adopted [the Court's] construction of the statute").

The conclusion that Congress ratified the longstanding judicial view of the Comstock Act is strongly reinforced by the Historical and Revision Note that was included in the 1945 report of the House Committee on the Revision of the Laws[12] when Congress enacted title 18 of the U.S. Code into positive law.[13] That Note subsequently was appended to the official U.S. Code entries for sections 1461 and 1462. *See* 18 U.S.C. § 1461 (Historical and Revision Note).[14] It specifically "invited" the "attention of Congress" to the courts of appeals' decisions in *Youngs Rubber*, *Davis*, *Nicholas*, and *One Package*, and quoted at length from *Youngs Rubber*, including its conclusion that the relevant provisions of the statute should be construed to require "an intent on the part of the sender that the article

[12] *See* H.R. Rep. No. 79-152, at A96–97 (1945).

[13] *See* Pub. L. No. 80-772, 62 Stat. at 768.

[14] The Historical and Revision Notes were written by a staff of experts hired by Congress to revise the U.S. Code in the 1940s, including the editorial staffs of the West and Thompson publishing companies, the former Chief of the Appellate Section of the Department of Justice Criminal Division, and other contributors from both inside and outside of government. *See* H.R. Rep. No. 79-152, at 1–7 (1945) (describing in detail this revision process and noting that "[t]he [House] Committee on Revision of the Laws has exercised close and constant supervision over this work through its general counsel . . . and its special counsel"). The Supreme Court has discussed or relied on Historical and Revision Notes numerous times, most frequently during the middle of the twentieth century. *See, e.g.*, *Ex parte Collett*, 337 U.S. 55, 65–71 (1949) (discussing a revision note to 28 U.S.C. § 1404 and concluding that the revision note was highly significant in determining the meaning of section 1404(a)); *W. Pac. R.R. Corp. v. W. Pac. R.R. Co.*, 345 U.S. 247, 254–55 (1953); *Muniz v. Hoffman*, 422 U.S. 454, 471–73 (1975).

mailed or shipped by common carrier be used for illegal contraception or abortion." *Id.*[15]

Congress subsequently amended the Comstock Act four times (in 1955, 1958, 1971, and 1994) without changing the language in any respect that suggested disagreement with the well-established narrowing interpretation that the Historical and Revision Note had specifically brought to its attention. Congress made the third of these amendments in 1971—removing the Act's references to contraceptives—after being informed by the Post-

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[15] The Note's complete discussion of the court of appeals decisions is as follows:

> The attention of Congress is invited to the following decisions of the Federal courts construing this section and section 1462 of this title.
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> In *Youngs Rubber Corporation, Inc. v. C. I. Lee & Co., Inc.*, C.C.A. 1930, 45 F. 2d 103, it was said that the word "adapted" as used in this section and in section 1462 of this title, the latter relating to importation and transportation of obscene matter, is not to be construed literally, the more reasonable interpretation being to construe the whole phrase "designed, adapted or intended" as requiring "an intent on the part of the sender that the article mailed or shipped by common carrier be used for illegal contraception or abortion or for indecent or immoral purposes." The court pointed out that, taken literally, the language of these sections would seem to forbid the transportation by mail or common carrier of anything "adapted," in the sense of being suitable or fitted, for preventing conception or for any indecent or immoral purpose, "even though the article might also be capable of legitimate uses and the sender in good faith supposed that it would be used only legitimately. Such a construction would prevent mailing to or by a physician of any drug or mechanical device 'adapted' for contraceptive or abortifacient uses, although the physician desired to use or to prescribe it for proper medical purposes. The intention to prevent a proper medical use of drugs or other articles merely because they are capable of illegal uses is not lightly to be ascribed to Congress. Section 334 [this section] forbids also the mailing of obscene books and writings; yet it has never been thought to bar from the mails medical writings sent to or by physicians for proper purposes, though of a character which would render them highly indecent if sent broadcast to all classes of persons." In *United States v. Nicholas*, C.C.A. 1938, 97 F. 2d 510, ruling directly on this point, it was held that the importation or sending through the mails of contraceptive articles or publications is not forbidden absolutely, but only when such articles or publications are unlawfully employed. The same rule was followed in *Davis v. United States*, C.C.A. 1933, 62 F. 2d 473, quoting the obiter opinion from *Youngs Rubber Corporation v. C. I. Lee & Co.*, *supra*, and holding that the intent of the person mailing a circular conveying information for preventing conception that the article described therein should be used for condemned purposes was necessary for a conviction; also that this section must be given a reasonable construction. (See also *United States v. One Package*, C.C.A. 1936, 86 F. 2d 737.)
>
> 18 U.S.C. § 1461 (Historical and Revision Note).

master General that both the federal courts and USPS had adopted this narrowing interpretation. *See* H.R. Rep. No. 91-1105, at 3–4 (1970).[16] Moreover, we have found no evidence that Congress disapproved of the interpretation.[17] Indeed, in 2007 Congress legislated regarding the FDA's treatment of mifepristone in a manner consistent with the understanding that the Comstock Act does not categorically prohibit the covered modes of conveying abortion-inducing drugs.[18]

Congress's several actions "perpetuating the wording" of the Comstock Act's abortion provisions against the backdrop of a well-established, settled judicial construction that was brought to Congress's attention

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[16] *See supra* note 11 (explaining that the courts of appeals' rationales applied equally to conveyance of items to prevent conception and to produce abortion).

[17] The House report stated at the outset of its discussion that "[e]xisting statutes completely prohibit the importation, interstate transportation, and mailing of contraceptive materials, or the mailing of advertisement or information concerning how or where such contraceptives may be obtained or how conception may be prevented." H.R. Rep. No. 91-1105, at 2. That introductory remark, however, plainly was a reference to the literal text of the provisions, as opposed to their settled meaning. The report proceeded to convey the Postmaster General's description of the settled judicial and administrative narrowing construction of the statute, noting that it was in tension with the text of the contraception provisions, and neither the report nor any evidence in the legislative record of which we are aware expresses the committee's disagreement with that construction.

[18] In approving a mifepristone product for certain abortions in 2000, the FDA imposed certain restrictions on distribution as a condition of approval, pursuant to its regulatory authority. *See* Letter for Sandra P. Arnold, Vice President, Population Council, from Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin., *Re: NDA 20-687* (Sept. 28, 2000). In the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Congress provided that any such restrictions, identified in the FDAAA as "elements to assure safe use," were deemed to be a "Risk Evaluation and Mitigation Strategy" that would continue to be required under the new statutory regime unless and until the FDA determined that modifications were necessary. *See* Pub. L. No. 110-85, tit. IX, § 909(b), 121 Stat. 823, 950–51 (2007). In the debate preceding this amendment, critics of the FDA's 2000 approval of mifepristone for abortion purposes acknowledged that the legislation would apply to that mifepristone approval. *See* 153 Cong. Rec. S5765 (daily ed. May 9, 2007) (statement of Sen. Coburn); 153 Cong. Rec. S5469–70 (daily ed. May 2, 2007) (statement of Sen. DeMint). Yet neither those critics nor anyone else in the congressional debate mentioned the Comstock Act, even though it would have been natural to assume that the FDA's 2000 approval had resulted in the distribution of mifepristone to certified physicians through the mail or by common carrier. Congress's decision to carry forward the FDA's regulatory conditions for mifepristone without addressing such modes of distribution suggests that Congress did not understand the Comstock Act to invariably prohibit the conveyance by mail or common carrier of drugs intended to induce abortions.

establishes Congress's acceptance of that narrowing construction. *Inclusive Cmtys. Project*, 576 U.S. at 536. That construction, as noted, does not prohibit the mailing of an item that is designed, adapted, or intended for producing abortion in the absence of an intent by the sender that the item will be used unlawfully.

C.

USPS has accepted the settled judicial construction of the Comstock Act—and reported as much to Congress.

In 1951, the Solicitor of the Post Office Department, Roy C. Frank, wrote to an Arizona postmaster concerning a Planned Parenthood clinic's mailing of diaphragms and vaginal jellies to its patients "for medicinal purposes." *Contraceptive Matter—Mailings—Physicians*, 9 Op. Sol. P.O.D. 47 (1951) (No. 40). Citing "the decisions of the Federal courts," Frank opined that a "mailing of contraceptives by a physician to a patient would not be regarded as a violation" of the Comstock Act. *Id.* Similarly, in 1963, when the St. Louis Postmaster detained 490 "contraceptive devices and substances," the USPS General Counsel informed him that he should "dispatch" those items because "there is no available evidence that the items in each of these parcels were being distributed for unlawful purposes." Letter for Harriet F. Pilpel, Greenbaum, Wolff & Ernst, from Louis J. Doyle, General Counsel, Post Office Department (Oct. 24, 1963) (on file with the Smith College Libraries). In a letter to the sender Emko Company's counsel, the USPS General Counsel added that "should we obtain evidence in the future that [Emko] is distributing contraceptive devices and substances for unlawful purposes we will again look into the matter." *Id.*

Of particular importance, when Congress was considering amendments to the Comstock Act in 1970, USPS brought to Congress's attention its acceptance of the Judiciary's narrowing construction. The Postmaster General submitted a statement to Congress about his agency's understanding that "the delivery by mail of contraceptive information or materials has by court decisions, and administrative rulings based on such decisions, been considered proper in cases where a lawful and permissive purpose is present." *See* H.R. Rep. No. 91-1105, at 3–4 (1970). As a result, "[t]he lawful mailing . . . of contraceptive articles . . . is dependent on the interpretation given to the intended purpose." *Id.* at 4. The Postmaster General noted that "[w]hat is a lawful purpose within the meaning

of the interpretations given, though vaguely identifiable, has with the passage of time also been considerably broadened" and that "many States . . . have adopted positive legislation to authorize or encourage public family planning services." *Id.* As a result, by the time the Postmaster General wrote to Congress in 1970—after the Court's *Griswold* decision holding unconstitutional a state prohibition on the use of contraception—"it [was] quite clear that the cited law as presently written [was] unenforceable." *Id.*

The House Ways and Means Committee included the Postmaster General's statement in its report on the draft amendment and noted that "[i]n view of" that statement—along with statements supporting the draft amendment by the Departments of Labor and of Health, Education, and Welfare—the Committee on Ways and Means was "unanimous in recommending enactment of H.R. 4605." *Id.* Congress then amended the Comstock Act to repeal most of the Act's applications to contraceptives. *See* Pub. L. No. 91-662, 84 Stat. at 1973–74.[19]

* * * * *

Thus, before the Court's recognition of a constitutional right to contraception in *Griswold* and to abortion in *Roe*, the Judiciary, Congress, and USPS itself all understood section 1461 and the related provisions of the Comstock Act not to prohibit the conveyance of articles intended for preventing conception or producing an abortion where the sender lacks the intent that those items should be used unlawfully. We further note that, shortly after Congress amended the Comstock Act in 1971 to eliminate the restrictions on contraceptives, the Supreme Court's decision in *Roe* effectively rendered unenforceable the restrictions on articles "designed, adapted, or intended for producing abortion." For the past half century, courts have not had the occasion to elaborate further on the meaning of the Comstock Act as it relates to abortion, including regarding

[19] Although the 1971 Congress eliminated the preexisting broad prohibitions on sending contraception-related articles and information using the mails or common carriage, it added a narrower prohibition designed to prevent the mailing of unsolicited contraceptive items and advertising to private homes. *See* 39 U.S.C. § 3001(e); *see also* 18 U.S.C. § 1461 (making it a crime to knowingly use the mails to mail anything deemed "nonmailable" in section 3001(e)). In *Bolger*, the Supreme Court held that the ban on unsolicited advertisements of contraceptives violates the First Amendment. 463 U.S. at 61.

the sources of law that inform whether an abortion would be "unlawful" for purposes of the established construction of the Act.

II.

In Part I we demonstrated that, in accord with the prevailing judicial construction Congress ratified, section 1461 does not prohibit the mailing of articles that can be used to produce abortion, including mifepristone and misoprostol, where the sender lacks the intent that those items should be used unlawfully.[20] We turn now to address the many circumstances in which a sender of these drugs typically will lack an intent that they be used unlawfully.

Federal law does not prohibit the use of mifepristone and misoprostol for producing abortions. Indeed, the FDA has determined the use of mifepristone in a regimen with misoprostol to be safe and effective for the medical termination of early pregnancy. And, to the extent relevant, these drugs can serve important medical purposes and recipients in every state can use them lawfully in some circumstances. This is true even when the drugs would be delivered to an address in a jurisdiction with restrictive abortion laws, because women who receive the drugs in all fifty states may, at least in some circumstances, lawfully use mifepristone and misoprostol to induce an abortion.

We note that those sending or delivering mifepristone and misoprostol typically will lack complete knowledge of how the recipients intend to use them and whether that use is unlawful under relevant law. Therefore, even when a sender or deliverer of mifepristone or misoprostol, including USPS, knows that a package contains such drugs—or indeed that they will be used to facilitate an abortion—such knowledge alone is not a sufficient basis for concluding that section 1461 has been violated. We also recognize that USPS may have reason to consider adopting uniform policies or practices regarding the mailing of mifepristone or misoprostol. *Cf. Smith v. United States*, 431 U.S. 291, 304 n.10 (1977) ("[T]he nationwide character of the postal system argues in favor of a nationally uniform construction of [section] 1461.").

[20] *See supra* note 3 (noting that the same test would apply to section 1462 and to recipients of the drugs to the extent those persons might be amenable to prosecution).

We have not undertaken the challenging task of a detailed review of state abortion laws, but we can offer some illustrative uses for mifepristone and misoprostol that the law of a given state would not prohibit:

- First, in most states—where a majority of the U.S. population lives—abortion continues to be lawful until at least twenty weeks' gestation. It is very unlikely that someone sending validly prescribed mifepristone or misoprostol into such states will intend for them to be used unlawfully.
- Second, even some states that in recent months have enacted or begun to enforce more restrictive abortion laws continue to allow abortion for at least some number of weeks of pregnancy. Use of mifepristone and misoprostol to terminate a pregnancy that falls within that period would be lawful.
- Third, thus far, no state that has enacted or newly begun to enforce restrictions on abortion in the wake of *Dobbs v. Jackson Women's Health Organization*, 142 S. Ct. 2228 (2022), prohibits abortions that are necessary to preserve the life of the woman.[21] Many medical conditions that make pregnancy potentially life-threatening—for instance, certain heart conditions, pulmonary hypertension, or Marfan Syndrome[22]—are known in the first trimester, when women most commonly use mifepristone and misoprostol to induce an abortion. Such a use of these drugs to terminate a life-threatening pregnancy would be lawful.
- Fourth, some state abortion restrictions also include exceptions for cases of rape or incest, to protect the health of the woman, or where there are severe fetal anomalies. The use of mifepristone or miso-

[21] *See Dobbs*, 142 S. Ct. at 2305 n.2 (Kavanaugh, J., concurring) ("Abortion statutes traditionally and currently provide for an exception when an abortion is necessary to protect the life of the mother."); *see also Roe*, 410 U.S. at 173 (Rehnquist, J., dissenting) ("[I]f [a state] statute were to prohibit an abortion even where the mother's life is in jeopardy, I have little doubt that such a statute would lack a rational relation to a valid state objective . . . .").

[22] *See, e.g.*, Inst. of Med., Clinical Prevention Services for Women: Closing the Gaps 103–04 (2011); *see also Burwell v. Hobby Lobby Stores, Inc.*, 573 U.S. 682, 737 (2014) (Kennedy, J., concurring) (noting that "[t]here are many medical conditions for which pregnancy is contraindicated").

prostol to produce an abortion in such cases would therefore be lawful.

- Fifth, some states that regulate the conduct of certain actors involved in abortions do not make it unlawful for the woman herself to abort her pregnancy. In those contexts, section 1461 might not prohibit the mailing of mifepristone and misoprostol to a woman in a state with restrictions on abortion, even if the sender does so with the intent that the woman use the drugs to produce an abortion.
- Sixth, even if a state prohibits a pregnant person from ingesting mifepristone or misoprostol for the purpose of inducing an abortion, such an individual has a constitutional right to travel to another state that has not prohibited that activity and to ingest the drugs there.[23] Someone sending a woman these drugs is unlikely to know where she will use them, which might be in a state in which such use is lawful.
- Seventh, federal agencies provide abortion services in some circumstances without regard to contrary state law.[24] Mailings of abortion

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[23] *See Dobbs*, 142 S. Ct. at 2309 (Kavanaugh, J., concurring) ("[M]ay a State bar a resident of that State from traveling to another State to obtain an abortion? In my view, the answer is no based on the constitutional right to interstate travel."); *id.* (referring to the question as "not especially difficult"); *see also Bigelow v. Virginia*, 421 U.S. 809, 824 (1975) (explaining that Virginia could not "prevent its residents from traveling to New York to obtain [abortion] services or . . . prosecute them for going there" (citing *United States v. Guest*, 383 U.S. 745, 757–59 (1966))).

[24] The Department of Veterans Affairs ("VA"), for example, recently has begun providing abortions to veterans and certain other VA beneficiaries without regard to state law when the life or health of the woman would be endangered if the pregnancy were carried to term or the pregnancy is the result of an act of rape or incest. *See* Reproductive Health Services, 87 Fed. Reg. 55,287, 55,288 (Sept. 9, 2022). "[S]tates may not restrict VA and its employees acting within the scope of their federal authority from providing abortion services as authorized by federal law, including VA's rule." *Intergovernmental Immunity for the Department of Veterans Affairs and Its Employees When Providing Certain Abortion Services*, 46 Op. O.L.C. __, at *10; *see also* 87 Fed. Reg. at 55,294 (noting that state and local laws, including criminal laws, that "restrict[], limit[], or otherwise impede[] a VA professional's provision of care permitted by" this new rule "would be preempted" (citing 38 C.F.R. § 17.419(b))). Also, the Department of Defense ("DoD") has for many years provided service members, dependents, and other beneficiaries of DoD health care services with abortion services when a pregnancy is the result of rape or incest or when continuing the pregnancy would endanger the woman's life, and DoD has indicated it will continue to do so without regard to contrary state laws. *See*

medications intended to be used pursuant to these federal authorities would be lawful under section 1461, because contrary state law could not constitutionally be applied.

- Finally, individuals use mifepristone and misoprostol for medical purposes other than to induce abortions and the legality of those uses would remain unaffected by state restrictions on abortion. For instance, the same dosages of mifepristone and misoprostol that are used for medication abortion can be used to treat a miscarriage,[25] and misoprostol is commonly prescribed for the prevention and treatment of gastric ulcers.[26]

Thus, no matter where the drugs are delivered, a variety of uses of mifepristone and misoprostol serve important medical purposes and are lawful under federal and state law. Accordingly, USPS could not reasonably assume that the drugs are nonmailable simply because they are being sent into a jurisdiction that significantly restricts abortion. Nor would such an assumption based solely on the recipient's address be reasonable even if it is apparent that some women in a particular state are using the drugs in question in violation of state law. *Cf. Youngs Rubber*, 45 F.2d at 110 (although the volume of the plaintiff's sales nationwide justified an inference that the drug stores to which the condoms were being delivered must have been selling at least some of them for purposes that were prohibited under state law—"and that plaintiff must know this"—that was insufficient to conclude that the company intended such illegal conduct by the recipients).

In conclusion, section 1461 does not prohibit the mailing of mifepristone or misoprostol where the sender lacks the intent that the recipient will use them unlawfully. And in light of the many lawful uses of mifepristone and misoprostol, the fact that these drugs are being mailed to a

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Memorandum for Senior Pentagon Leadership from Gilbert R. Cisneros, Jr., Under Secretary of Defense for Personnel and Readiness, Department of Defense, *Re: Ensuring Access to Essential Women's Health Care Services for Service Members, Dependents, Beneficiaries, and Department of Defense Civilian Employees* (June 28, 2022).

[25] *See, e.g.*, Honor Macnaughton, Melissa Nothnagle & Jessica Early, *Mifepristone and Misoprostol for Early Pregnancy Loss and Medication Abortion*, 103 Am. Fam. Physician 473, 475 (Apr. 15, 2021).

[26] *See Cytotec Misoprostol Tablets*, U.S. Food & Drug Admin. 5–6 (Aug. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019268s051lbl.pdf (misoprostol label).

jurisdiction that significantly restricts abortion is not a sufficient basis for concluding that the mailing violates section 1461.[27]

CHRISTOPHER H. SCHROEDER
Assistant Attorney General
Office of Legal Counsel

[27] While this request was pending, we received a similar request from the Department of Health and Human Services ("HHS") regarding the Comstock Act in connection with the Food and Drug Administration's Risk Evaluation and Mitigation Strategy for mifepristone. We conveyed our conclusions by e-mail to HHS on December 19, 2022, and we noted there that this memorandum was forthcoming. E-mail for Samuel Bagenstos, General Counsel, HHS, from Christopher H. Schroeder, Assistant Attorney General, Office of Legal Counsel, *Re: Advice Regarding Comstock* (Dec. 19, 2022, 8:31 PM).

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

Alliance for Hippocratic Medicine, *et al.*, Plaintiffs, v. U.S. Food and Drug Administration, *et al.*, Defendant.	Case No. 2:22-cv-00223-Z

DECLARATION OF JASON LINDO

I, Jason Lindo, Ph.D., pursuant to 28 U.S.C. § 1746, declare under penalty of perjury that the following is true and correct.

I. Professional Credentials and Experience

1. I provide the following facts and opinions as an expert in the field of economics, policy evaluation, and reproductive health care. I am a Professor of Economics and the Ray A. Rothrock '77 Senior Fellow at Texas A&M University. Prior to my appointment as full professor on September 1, 2018, I was an Associate Professor of Economics at Texas A&M beginning in 2013.

2. I have been a Research Associate at the National Bureau of Economic Research (NBER) since 2014, and before that, I was a Faculty Research Fellow at NBER beginning in 2011. NBER is the nation's leading nonprofit economic research organization, studying a wide range of topics, including the effects of various public policies.

3. I received a B.A. in economics in 2004, an M.A. in economics in 2005, and a Ph.D. in economics in 2009—all from the University of California, Davis.

4. I have published 28 research articles in peer-reviewed journals and books. I am a Specialized Co-editor of *Economic Inquiry*, in which role I determine whether the journal should publish submitted papers in the areas of health economics, public economics, and policy evaluation.

5. My research interests include health economics and issues concerning youth, including the economic effects of abortion and contraceptive policies. My recent and ongoing work is especially focused on documenting the effects of changes in access to reproductive healthcare.

6. I have taught courses on empirical research methods at the undergraduate and graduate levels for 13 years. These courses focus on the quantitative methods that economists use to evaluate the causal effects of government programs and other interventions, how these methods overcome problems that often plague correlational analyses, and the conditions under which these methods are appropriate. They also cover how these methods are used in the context of research on reproductive health care.

7. A copy of my curriculum vitae setting forth my experience, education, and credentials in greater detail is attached as **Exhibit A**.

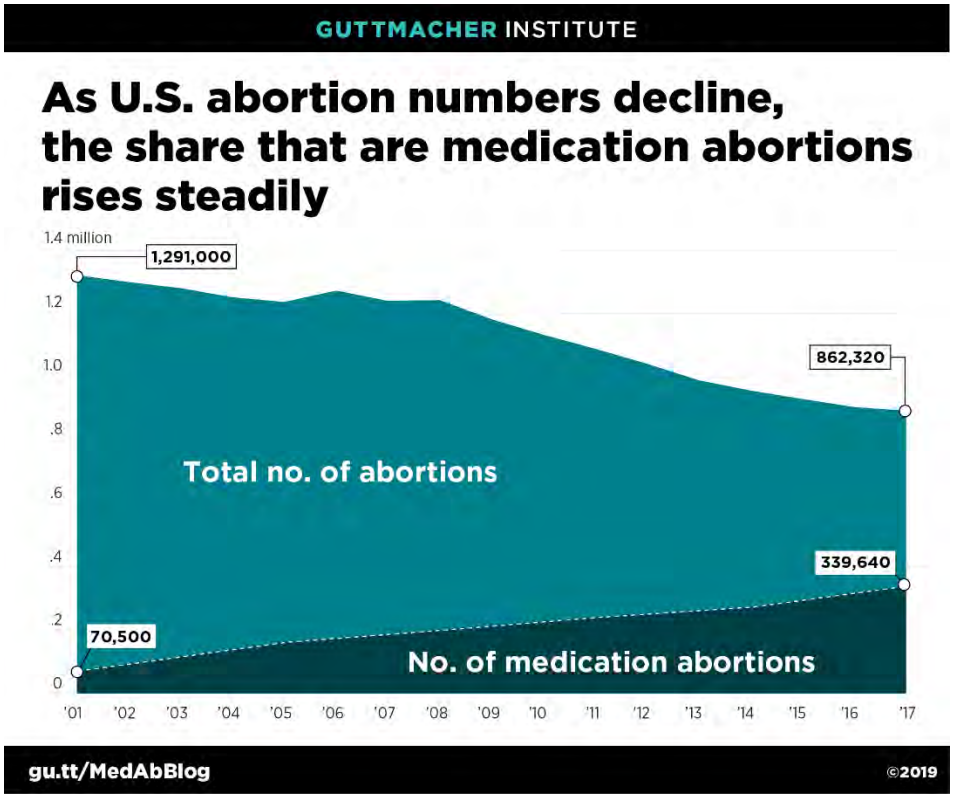
II. Summary of Findings Below

8. Individuals seeking abortions in the United States come from an extremely diverse set of backgrounds. Nonetheless, a substantial majority have incomes below the federal poverty line, a majority have prior children, and a majority are neither married nor cohabitating.

9. Individuals report seeking abortions for many different reasons and combinations of reasons. The most frequently cited reasons, which have substantial overlap, include: financial insecurity, poor timing and/or not being ready, educational and career plans, problems associated

with their partners, concerns about their existing children, and concerns about health that would arise from continuing the pregnancy.

10. The Food and Drug Administration approved mifepristone for use in 2000. Since 2000, the overall number of abortions in the United States has decreased substantially. Though the number of abortions is decreasing, the proportion of people who do obtain abortions who opt for a medication abortion is increasing. This is shown in the figure below (and discussed in greater detail in a subsequent section).



11. The share of abortions that are medication abortions has grown especially quickly in recent years. Today, over 50 percent of abortions are medication abortions.

12. As detailed below, informational resources provided to abortion patients typically highlight that the choice to have a medication abortion or a surgical abortion is a personal decision, and that there are many reasons why people with different preferences may choose one

method over the other.[1] These informational resources often include among the advantages of medication abortion such factors as: it is less physically invasive (i.e., eliminates the need to have a procedure in which a doctor inserts surgical instruments into the uterus); it is more private; and it allows greater control over when, where, and with whom the abortion occurs. Surveys of patients presenting for abortion at clinics where they could obtain either a medication abortion or a surgical abortion also highlight these factors, among many others, as important in influencing people's preferences for medication abortion.

13. People may also obtain a medication abortion, rather than a surgical abortion, because medication abortion is the only option offered by a provider that is accessible to them. This is particularly relevant given that 31 percent of clinics providing abortion *only* provide medication abortion and because people seeking abortions, particularly surgical abortions, face many obstacles to obtaining care, including obstacles related to travel. It is also relevant because medication abortions are available, at least in some circumstances, via telehealth, whereas surgical abortions are not.

14. The American College of Obstetricians and Gynecologists also highlights that certain medical conditions may make medication abortion preferable.[2]

15. Given the large number of abortion patients who have medication abortions and their clearly articulated needs and/or informed reasons for doing so, removing medication abortion as an option would represent a shift that is substantially detrimental to a very large share of individuals seeking abortions. It would prevent many individuals from choosing the method

[1] Here and below, I use "medication abortion" to refer to the typical practice used in the United States of administering mifepristone to stop a pregnancy from progressing followed by misoprostol to expel the contents of the uterus.

[2] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology, Society of Family Planning. Medication Abortion Up to 70 Days of Gestation: ACOG Practice Bulletin, Number 225. Obstet Gynecol. 2020 Oct;136(4):e31-e47. doi: 10.1097/AOG.0000000000004082. PMID: 32804884.

that is best for them given their own health or other needs and/or preferences. Others will be made worse off still because some abortion providers and locations will no longer be available to them—i.e., if their closest or preferred clinic is only equipped to provide medication abortion. As a result, for some of these individuals, financial and logistical constraints will delay their ability to obtain an abortion. For others, it will make them unable to obtain an abortion.

16. Those seeking abortions will also be made worse off by the broader effect on the landscape for abortion care. Though the effect will be less than one-for-one, the demand for surgical abortions will increase if people can no longer obtain medication abortions. Many factors will prevent abortion providers from meeting a large and sudden increase in demand for surgical abortions, including infrastructure and staffing. As a result, the increase in demand for surgical abortions is expected to increase waiting times for *all* individuals seeking abortions (not just those with a preference for medication abortions).

17. Abortion providers often provide many other forms of health care, including contraception, sexually transmitted infections ("STI") screening, clinical breast exams, etc. A surge in demand for them to provide surgical abortions could impair their ability to provide such care, which could have detrimental impacts on their other patients.

18. Increased waiting times for abortion will cause delays such that some people will have abortions at later stages of pregnancy and some will be prevented from obtaining abortions at all. For those who have delayed abortions, the financial consequences can be devastating because: (i) a large share of individuals seeking abortion have low incomes, (ii) the cost of an abortion very early in pregnancy is already so high that it would be classified as a catastrophic health expenditure[3] for most *middle*-income individuals, and (iii) the cost of obtaining an

[3] The term "catastrophic health expenditure" generally refers to circumstances in which the out-of-pocket cost of a health service is above 40 percent of nonsubsistence income, where nonsubsistence income is income minus the

abortion increases significantly with the gestational age of the fetus. Delayed abortions may also increase the risk that a person's privacy is compromised in a way that harms them, *e.g.*, by increasing the likelihood that their pregnancy becomes apparent to others. Delays in abortion access will also place people at a greater risk of complications; while abortion is generally considered by the medical community to be extremely safe at any point and also to be safer than childbirth, the risks increase as pregnancy progresses.[4]

19. Increased waiting times will also prevent some people from having an abortion altogether. This will cause heightened health risks associated with continuing the pregnancy to childbirth.[5] Rigorous quantitative research detailed further below indicates that it will also reduce their earnings, increase poverty and/or depth of poverty, increase other measures of financial distress, reduce levels of education, and increase domestic violence.

20. Rigorous quantitative research also indicates that there will be extensive effects on the children of people who seek but are unable to obtain an abortion. As a result of the impacts on their parents, these children are expected to do worse in school (lower test scores and increased grade repetition), to have more behavioral and social issues, and ultimately to attain lower levels of completed education. They are also expected to have lower earnings as adults, poorer health, and an increased likelihood of criminal involvement.

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minimum amount that is needed to pay for basic necessities (food, childcare, health, housing, transportation, taxes, clothing, and personal items). It is a commonly used measure of the severity with which the expenditure will impoverish a household.

[4] See, e.g., Bartlett LA, Berg CJ, Shulman HB, Zane SB, Green CA, Whitehead S, Atrash HK. Risk factors for legal induced abortion-related mortality in the United States. Obstet Gynecol. 2004 Apr;103(4):729-37. doi: 10.1097/01.AOG.0000116260.81570.60. PMID: 15051566; Frick AC, Drey EA, Diedrich JT, Steinauer JE. Effect of prior cesarean delivery on risk of second-trimester surgical abortion complications. Obstet Gynecol. 2010 Apr;115(4):760-764. doi: 10.1097/AOG.0b013e3181d43f42. PMID: 20308836; Grimes DA, Schulz KF, Cates WJ Jr. Prevention of uterine perforation during curettage abortion. JAMA. 1984 Apr 27;251(16):2108-11. PMID: 6708260.

[5] See, e.g., Raymond EG, Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol. 2012 Feb;119(2 Pt 1):215-9. doi: 10.1097/AOG.0b013e31823fe923. PMID: 22270271.

21. Ceasing to allow medication abortion will also impact the lives of the many individuals who choose to own, operate, and work for businesses that provide abortion care because it restricts their ability to provide care to people in a manner that is consistent with their medical judgment about what is the most appropriate method for providing the health care sought. It is also important to note that "burnout" is frequently cited among those who stop working for abortion providers (and for health care providers generally), and heightened stress may occur when providers are operating at their full capacity and trying to expand that capacity, or when they are otherwise forced to provide health care in a manner that does not align with their medical judgment and/or with their patients' needs and preferences. Moreover, for at least some providers and clinics who only offer medication abortion, eliminating medication abortion would eliminate their ability to provide abortions altogether, and for others it would require them to undertake substantial changes to their practice.

22. Many of these issues clearly concern the broader public. Among the issues not touched on above, in the event medication abortion were to become unavailable, the broader public is expected to face: increased health care costs due to increased health care utilization; increased taxes due to increased reliance on public assistance and social safety net programs; and general exposure to poverty, which is pervasive, hard to escape, and often persists from one generation to the next.

23. Overall, eliminating medication abortion will limit people's ability to make choices about their life and health, including how and when to have children. Those with limited economic resources, privacy and safety concerns, and women of color are disproportionately likely to be affected in this manner. This will have far-reaching impacts on individuals seeking abortion and their families; those who own, operate, and work for abortion providers; and the

broader public.

24. These are the effects that can be expected if medication abortion ceases to be available in the United States, based on the extensive scientific literature spanning various disciplines.

III. Background

25. In this section, I provide background on individuals seeking abortions in the United States. An important caveat to this background, however, is that, in the wake of the Supreme Court overturning *Roe v. Wade*, the landscape has changed in ways that researchers are still in the process of documenting.

III.A. Background on Individuals Seeking Abortion Generally

26. Based on 2014 abortion rates: 23.7 percent of women aged 15-44 years in 2014 were expected to have an abortion by the time they turned 45 years old (assuming 2014 abortion rates were to continue through the time they turned 45 years old);[6] 12 percent of people obtaining abortions were less than 20 years old; and 60 percent were in their 20s.[7] People of color are disproportionately represented among those obtaining abortions. In terms of race, 27.6 percent of people obtaining abortions in 2014 were Black, even though only 14.9 percent of US women aged 15-44 were Black.[8] In terms of ethnicity, 24.8 percent of individuals obtaining abortions in 2014 were Hispanic, even though only 20 percent of US residents were Hispanic.[9]

27. A substantial majority of those seeking abortions have relatively low incomes.[10] In 2014, half had incomes less than the federal poverty line and three-quarters had incomes less

[6] Rachel K. Jones & Jenna Jerman, *Population Group Abortion Rates and Lifetime Incidence of Abortion: United States, 2008–2014*, 107 AM. J. PUB. HEALTH 1904, 1907 (2017).
[7] *Id.* at 1906.
[8] *Id.*
[9] *Id.*
[10] *Id.* at 1906–1907.

than 200 percent of the poverty line.[11,12] Compounding their financial difficulties, 59 percent had previously given birth and 55 percent were neither married nor cohabiting.[13] Moreover, 55 percent reported having experienced at least one "disruptive life event" during the preceding 12 months, where disruptive life events include the death of a close friend or family member, having a family member with a serious health problem, having a baby, separating from a partner, having a partner arrested or incarcerated, being unemployed for at least one month, falling behind on rent or a mortgage, or moving two or more times.[14]

28. Individuals report seeking abortions for many different reasons and combinations thereof. Most (64 percent) report multiple and/or overlapping reasons.[15] 40 percent report financial concerns.[16] 36 percent report concerns about the timing and/or not being ready.[17] 20 percent report concerns that continuing the pregnancy would interfere with their future goals, usually involving school (14 percent) and/or career plans (7 percent).[18] 31 percent report varied concerns associated with their partner, including poor and/or unstable relationships, a lack of support, and/or that the man involved in the pregnancy is the "wrong guy" or is abusive.[19] Individuals with abusive partners report concerns that continuing an unwanted pregnancy will

[11] In 2014, the Federal Poverty line was $12,316 for a single adult, $16,317 for a family with one adult and one child, and $19,073 for a family with one adult and two children. The Federal Poverty line was $15,853 for family of two adults, $19,055 for a family with two adults and one child, and $24,008 for a family with two adults and two children. CARMEN DENAVAS-WALT & BERNADETTE D. PROCTOR, U.S. CENSUS BUREAU, INCOME AND POVERTY IN THE UNITED STATES: 2014 43 (2015).
[12] Jones, *supra* note 6, at 1906.
[13] *Id*.
[14] Rachel K. Jones & Jenna Jerman, *Characteristics and Circumstances of U.S. Women Who Obtain Very Early and Second Trimester Abortions*, 12 PLOSONE 1, 3–4 (2017).
[15] M Antonia Biggs, H. Gould & Diana Greene Foster, *Understanding why women seek abortions in the US*, 13 BMC WOMEN'S HEALTH 29 (2013).
[16] *Id*.
[17] *Id*.
[18] *Id*.
[19] *Id*.

put them at greater risk by tethering them to their abuser.[20] 29 percent report concerns associated with their other children. 6 percent report concerns about their own health, including physical ailments and mental health problems that would be exacerbated by continuing the pregnancy.[21] 5 percent reported reasons associated with drug, tobacco, or alcohol use.[22]

29. An individual's ability to obtain an abortion depends on many factors beyond their control, including the availability of care, the amount of travel required, affordability, and state requirements such as waiting periods.[23] Survey data shows that among women who would have preferred to have obtained their abortions sooner in time, 59 percent report that delays occurred because it took time for them to make arrangements.[24] Consistent with this statistic, empirical evidence indicates that regulations that substantially increase the financial, travel, and/or logistical burdens of obtaining an abortion have a significant effect on abortion access.

III.B. Background on Medication Abortion

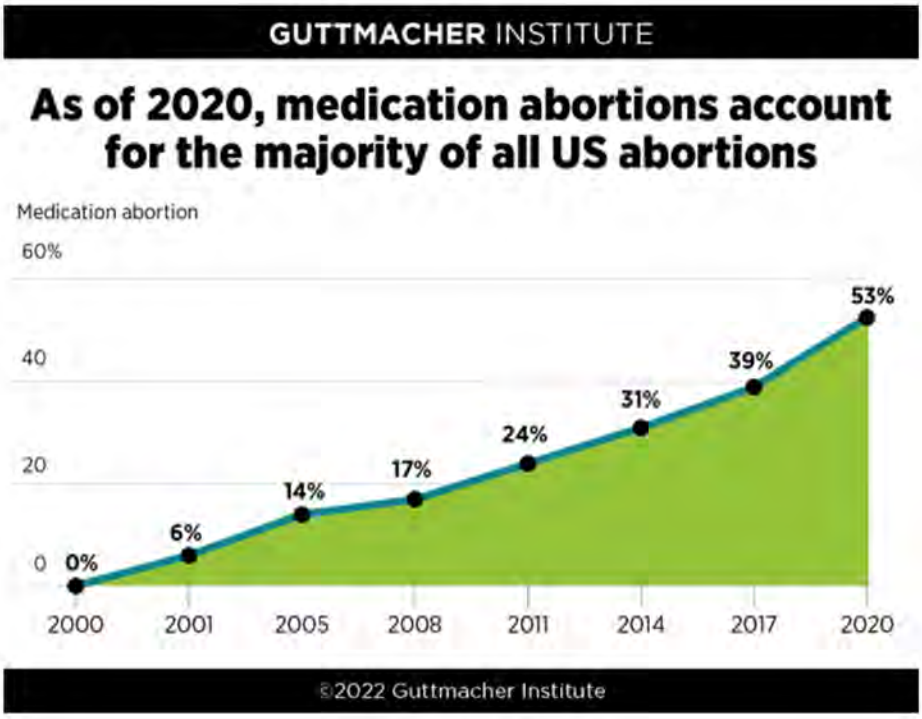
30. Since the Food and Drug Administration approved mifepristone (200 mg) for the medical termination of early intrauterine pregnancy in 2000, the number of medication abortions and the share of abortions that are medication abortions have grown consistently even though the number of abortions overall has fallen. The share of abortions that are medication abortions has grown especially quickly in recent years. Today, over 50 percent of abortions are medication abortions.

31. Data from both the Guttmacher Institute and the Centers for Disease Control and

[20] Karuna S. Chibber, M Antonia Biggs, Sarah C. M. Roberts & Diana Greene Foster, *The role of intimate partners in women's reasons for seeking abortion*, WOMENS HEALTH ISSUES, (2014).
[21] M Antonia Biggs, H. Gould & Diana Greene Foster, *Understanding why women seek abortions in the US*, 13 BMC WOMEN'S HEALTH 29 (2013).
[22] *Id*.
[23] NAT'L ACAD. SCI., THE SAFETY AND QUALITY OF ABORTION CARE IN THE UNITED STATES 12 (2018).
[24] Lawrence B. Finer et al., *Timing of Steps and Reasons for Delays in Obtaining Abortions in the United States*, 74 CONTRACEPTION 334, 335 (2006).

Prevention (CDC) support these statements. Data from both sources are commonly used among researchers (myself included) and are generally considered reliable. The Guttmacher Institute collects data on abortion incidence and service availability via surveys of all facilities known to have provided abortion services in the United States as a part of their Abortion Provider Census. The CDC collects aggregated data on abortion incidence based on requests to the central health agencies for the 50 states, the District of Columbia, and New York City.[25]

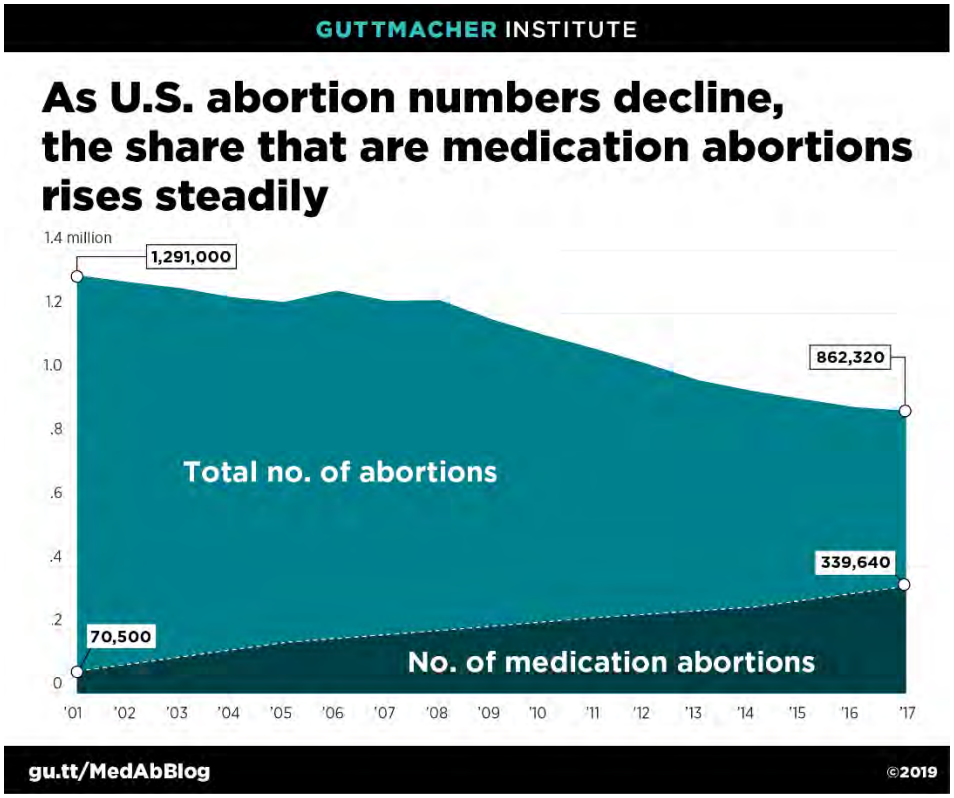
32. The figure below from the Guttmacher Institute shows that the share of medication abortions—as a percentage of abortions overall—has grown over time.[26] It also shows that this share has grown especially rapidly in recent years.



33. The following figure, which was shown above at ¶10, is based on Abortion

[25] My understanding is that the CDC requests data from New York City (apart from requesting aggregate data from the state of New York) because they recognize that New York City is so large (in population) that it can be particularly useful for researchers to have access to statistics for its residents.
[26] Rachel K. Jones *et al.*, *Medication Abortion Now Accounts for More Than Half of All US Abortions*, The Guttmacher Institute (February 24, 2022), https://www.guttmacher.org/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions

Provider Censuses. It shows that the overall *number* of medication abortions grew from 2001 to 2017 even as the number of abortions overall declined over this period.



34. Subsequently published data shows a significant increase in the overall number of medication abortions between 2017 and 2020. In particular, that number grew from 339,650 to 493,320, representing a 45 percent increase.[27]

35. CDC data for states reporting data corroborates these patterns. In 2020, 51.0 percent of abortions were defined as "early medical abortions" by the CDC (i.e., medication abortions at less than or equal to nine weeks gestation and typically involving the use of mifepristone followed by misoprostol).[28] The same CDC data also highlights a recent significant increase in the proportion of medication abortions, reporting that the percentage of all abortions

[27] Jones, RK, Kirstein, M, Philbin, J. Abortion incidence and service availability in the United States, 2020. *Perspect Sex Reprod Health*. 2022; 54(4): 128- 141. doi:10.1363/psrh.12215.
[28] Kortsmit K, Nguyen AT, Mandel MG, et al. Abortion Surveillance — United States, 2020. MMWR Surveill Summ 2022;71(No. SS-10):1–27. DOI: http://dx.doi.org/10.15585/mmwr.ss7110a1

performed by early medical abortions increased 22 percent from 2019 to 2020.[29]

36. Medication abortions are especially prevalent as a share of abortions at earlier stages of pregnancy. At less than or equal to six weeks gestation, 67.9% of abortions are medication abortions.[30] At 7 to 9 weeks gestation, 58.7% of abortions are medication abortions.[31]

37. There are many differences between medication abortion and surgical abortion that may cause a person to obtain a medication abortion rather than a surgical abortion.

38. One simple reason that people may prefer medication abortion is access. *31 percent of clinics offering abortion provide only medication abortion.* As a result, for many people seeking abortions, surgical abortion providers are more difficult, and in some cases impossible, for the pregnant person to visit. Given that individuals seeking abortions report financial, logistical, and transportation-related challenges to obtaining care,[32] some of these individuals may not be able to reach a surgical abortion provider and others may opt for the provider that presents fewer difficulties for obtaining a timely abortion. Along similar lines, people may prefer medication abortion because it is accessible to them via a telehealth visit whereas surgical abortion requires an in-person visit. The importance of access is underscored by extensive research documenting numerous obstacles (e.g., finding a facility, costs, travel, being turned away from a facility, etc.) that delay and/or prevent people from accessing abortion care.[33]

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[29] *Id*.
[30] *Id*.
[31] *Id*.
[32] See, e.g., Wingo, E., Ralph, L. J., Kaller, S., & Biggs, M. A. (2021). Abortion method preference among people presenting for abortion care. *Contraception*, *103*(4), 269-275; White, K., Grossman, D.,& Turan, J. M. (2016). Experiences accessing abortion care in Alabama among women traveling for services. Women's Health Issues, 26(3), 298-304; White, K., Turan, J. M., & Grossman, D. (2017). Travel for abortion services in Alabama and delays obtaining care. Women's Health Issues, 27(5), 523-529.
[33] See, e.g., Diana Greene Foster, *The Turnaway Study: Ten Years, a Thousand Women, and the Consequences of Having—or Being Denied—an Abortion* (2020); Wingo, E., Ralph, L. J., Kaller, S., & Biggs, M. A. (2021). Abortion method preference among people presenting for abortion care. *Contraception*, *103*(4), 269-275. https://doi.org/10.1016/j.contraception.2020.12.010

39. Some people may also prefer a medication abortion because it is the only option offered by a provider that they are comfortable with, based on a history of other care they have received from that provider,[34] which might include general health care, gynecological care, prenatal or obstetric care, or many other types of care other than abortion services.[35]

40. Organizations and health care providers seeking to educate people on abortion underscore the fact that preferences vary across individuals and that there are good reasons why—if given the choice—one might choose a medication abortion over a surgical abortion (or vice versa). Resources reviewing the pros and cons typically highlight that individuals may prefer a medication abortion based on factors such as: to avoid a procedure in which a doctor inserts surgical instruments into the uterus through the vagina; out of concerns for privacy; and because it gives them greater control over the when, where, and with whom the abortion occurs.[36]

41. In terms of concerns about privacy, it is important to note that surgical abortions can require a patient to have an escort home, which may be undesirable for individuals who would prefer to maintain their privacy or those who cannot find an escort they are comfortable with at the same time they can obtain a surgical abortion. Medication abortions may also help patients maintain their privacy because they require less time in the clinic (or no time in the clinic for individuals obtaining medication abortion via telehealth).

42. The ability to spend less time at the provider may also be important to individuals

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[34] Shochet T, Trussell J. Determinants of demand: method selection and provider preference among US women seeking abortion services. Contraception. 2008 Jun;77(6):397-404. doi: 10.1016/j.contraception.2008.02.003. Epub 2008 Apr 18. PMID: 18477487; PMCID: PMC5515366.

[35] Witwer E, Jones RK, Fuentes L, Castle SK. Abortion service delivery in clinics by state policy climate in 2017. Contracept X. 2020;2:100043. doi: 10.1016/j.conx.2020.100043. Epub 2020 Oct 16. PMID: 33083783; PMCID: PMC7561526.

[36] See, e.g., https://www.abortionfinder.org/abortion-types/pill-vs-procedure-how-to-decide (last accessed 1/12/23), https://www.ucsfhealth.org/education/aspiration-versus-medication-abortion (last accessed 1/12/23), and https://floridaabortion.com/2019/03/05/compare-medical-abortion-to-surgical-abortion/ (last accessed 1/12/23).

who have trouble getting time off work, those with COVID-19 concerns, those who are in school, and those who have children or other family members to care for.

43. Naturally, a person may find it more comfortable to have a medication abortion outside of the clinic context, at their own home, at a family member or friend's house, or at some other place of their choosing. Such preferences could be driven by stigma associated with abortion, hostile protestors, or more general preferences to be in an alternative setting with specific people.

44. Surveys of people presenting at clinics providing both surgical and medication abortions—at stages of pregnancy allowing them to have either type—shed light on the frequency with which some of these preferences (besides access) come into play. Noting that people often report multiple reasons and/or have overlapping reasons for choosing a medication abortion: 34 percent report so that it occurs at home,[37] 21 percent report emotional reasons, [38] 20 percent report a desire to avoid surgery, [39] 20 percent report that the medication abortion is less invasive, [40] 19 percent report that it is less scary, [41] 19 percent report that it feels more natural, [42,43] 17 percent report that it is safer, [44] 16 percent report that it is cheaper, [45] 16 percent report that it is easier, [46] and 13 percent report that it requires less time at the clinic.[47]

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[37] Shochet T, Trussell J. Determinants of demand: method selection and provider preference among US women seeking abortion services. Contraception. 2008 Jun;77(6):397-404. doi: 10.1016/j.contraception.2008.02.003. Epub 2008 Apr 18. PMID: 18477487; PMCID: PMC5515366.
[38] *Id*.
[39] *Id*.
[40] *Id*.
[41] *Id*.
[42] *Id*.
[43] It is not unusual for descriptions of medication abortion to use this terminology as a shorthand for conveying the idea that the process has many similarities with an early miscarriage.
[44] Shochet T, Trussell J. Determinants of demand: method selection and provider preference among US women seeking abortion services. Contraception. 2008 Jun;77(6):397-404. doi: 10.1016/j.contraception.2008.02.003. Epub 2008 Apr 18. PMID: 18477487; PMCID: PMC5515366.
[45] *Id*.
[46] *Id*.
[47] *Id*.

45. In addition, the American College of Obstetricians and Gynecologists Practice Bulletin explains that a person's medical conditions could make a medication abortion preferable, including "uterine fibroids that significantly distort the cervical canal or uterine cavity, congenital uterine anomalies, or introital scarring related to infibulation."[48]

IV. Expected effects of eliminating access to medication abortions

46. As I will discuss in the subsequent sections, eliminating access to medication abortions would likely affect these individuals—and others seeking abortions—by causing further restrictions on an individual's ability to choose whether, when, and where to have an abortion, which will in turn have material effects on the individual and society.

IV.A. The Unavailability of Medication Abortions Will Increase Waiting Times for Abortion and Other Forms of Care

47. Some of the individuals prevented from obtaining medication abortion from health care providers will end up having no abortion at all, and others will attempt to access abortion through other, less safe means. For some, this will include attempting to self-manage their abortions in the absence of access to a healthcare provider who can provide and counsel the pregnant person with respect to the abortion that the pregnant person needs.

48. Many of the individuals prevented from obtaining medication abortions will seek out surgical abortions. However, many factors will prevent abortion providers from meeting a large and sudden increase in demand for surgical abortions, including infrastructure and staffing.

49. As a result, the increase in demand for surgical abortions is expected to increase waiting times for abortion, which is typical in circumstances in which demand exceeds supply. In evaluating the number of people who will be affected by a restriction on medication abortion, it

[48] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology, Society of Family Planning. Medication Abortion Up to 70 Days of Gestation: ACOG Practice Bulletin, Number 225. Obstet Gynecol. 2020 Oct;136(4):e31-e47. doi: 10.1097/AOG.0000000000004082. PMID: 32804884.

is important to highlight that this impact will go well beyond the set of individuals who are prevented from obtaining medication abortions. It will affect *all* individuals seeking abortions, since those individuals will all be forced to seek out services from the significantly more limited number of providers who provide surgical abortions and also because providers offering surgical abortions have a limited capacity to provide such abortions.

50. For similar reasons, a surge in demand for surgical abortions could have spillover effects onto people seeking other forms of health care that some practitioners provide in addition to abortion. Abortion providers often also provide other health care services, including contraception, STI screening, clinical breast exams, etc. Given that these providers have constraints on the overall services they can provide (due to infrastructure and staffing), an increase in demand for any one service may strain their ability to provide other services. Thus, individuals who would typically obtain non-abortion care from an abortion provider may be impaired from obtaining such care.

IV.B. Effects of Increased Waiting Times: Delays and Prevented Abortions

51. Increased waiting times at abortion providers can delay or prevent individuals from obtaining abortions.[49] Increased waiting times can also cause individuals to alter where they obtain an abortion, as they attempt to find alternative providers with shorter waiting times. These effects make individuals worse off (relative to their circumstances if medication abortions are allowed) because the restriction is preventing them from making the choice that they determine is best for them, their health, and their families.

52. Moving beyond the general notion of choice, it is important to highlight that the increased waiting times will likely have devastating financial consequences. Below I will first

[49] Here and elsewhere I refer to a "delay" as a circumstance in which a person has an abortion later than they would otherwise if medication abortions were still allowed.

discuss how this is the case for individuals who ultimately obtain an abortion and then discuss how this is the case for individuals who continue their pregnancies to childbirth as a result of the increased difficulty of accessing abortion.

53. Most abortion patients across the United States pay out-of-pocket for abortion costs.[50] In 2020, the median cost of a first-trimester abortion was approximately $565, but varied across different regions with generally higher costs in the Northeast and the West.[51] The costs of second-trimester surgical abortions vary greatly depending on the gestation of the pregnancy. The overall average cost of a second trimester abortion is $895, but the average cost is $2000 later in the second trimester.[52,53]

54. As a result of these differences, increased waiting times will increase the fees people must pay for an abortion by causing them to get abortions later in pregnancy. A one-day delay can increase fees by $175.[54] Increased waiting times, and delays associated with them, may also increase the fees a person must pay by limiting the set of providers from which an individual can obtain care. Moreover, because increased waiting times and delays associated with them typically increase the amount of travel required to obtain a timely abortion, *overall* costs could rise further because of additional costs associated with transportation, childcare, lost wages, or lodging.[55]

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[50] Upadhyay UD, Ahlbach C, Kaller S, Cook C, Muñoz I. Trends In Self-Pay Charges And Insurance Acceptance For Abortion In The United States, 2017-20. Health Aff (Millwood). 2022 Apr;41(4):507-515. doi: 10.1377/hlthaff.2021.01528. PMID: 35377750.
[51] *Id.*
[52] Lindo, J. M., & Pineda-Torres, M. (2021). New Evidence on the Effects of Mandatory Waiting Periods for Abortion. *Journal of Health Economics*, *80*, 102533. https://doi.org/10.1016/j.jhealeco.2021.102533.
[53] See: https://www.plannedparenthood.org/learn/ask-experts/how-much-does-an-abortion-cost. (Last accessed December 28, 2022.)
[54] Lindo, J. M., & Pineda-Torres, M. (2021). New Evidence on the Effects of Mandatory Waiting Periods for Abortion. *Journal of Health Economics*, *80*, 102533. https://doi.org/10.1016/j.jhealeco.2021.102533.
[55] A full accounting of travel costs needs to take into consideration direct expenses, child care costs, and lost wages. See, e.g., Lindo, J. M., & Pineda-Torres, M. (2021). New Evidence on the Effects of Mandatory Waiting Periods for Abortion. *Journal of Health Economics*, *80*, 102533. https://doi.org/10.1016/j.jhealeco.2021.102533.

55. Here it is important to keep in mind that half of the people having abortions have incomes less than the federal poverty line.[56] Thus, a significant share of people having abortions do not have sufficient incomes to meet their basic needs (such as food, housing, and transportation). Additional expenses, or unexpected expenses, can put individuals in such households in even more perilous positions.

56. Research on the out-of-pocket costs in 2016 indicate that a first-trimester abortion would be classified as a catastrophic health expenditure [57] for individuals in households earning their state's median income for individuals living in 39 states, and second-trimester abortions would be a catastrophic health expenditure for individuals in households earning their state's median income for individuals living anywhere in the United States.[58] Given that a substantial majority of people seeking abortions are from low-income households rather than median-income households, the out-of-pocket costs for any type of abortion is likely to be a catastrophic health expenditure for a substantial majority of people seeking abortions.

57. Consistent with these statistics, research has shown that people forgo food and other basic necessities, take out payday and other loans, miss bills and rent, and pawn personal belongings in order to pay for abortions.[59]

58. There are also several non-monetary costs of delays that may be relevant to people seeking abortions. These non-monetary costs include: a heightened risk that their privacy is compromised, which could lead to abuse; psychological distress associated with having to wait; psychological distress associated with a more limited set of provider options (which could

[56] Jones, *supra* note 6, at 1906.
[57] *See supra* note 3 (providing definition of "catastrophic health expenditure").
[58] Zuniga C, Thompson TA, Blanchard K. Abortion as a Catastrophic Health Expenditure in the United States. Womens Health Issues. 2020 Nov-Dec;30(6):416-425. doi: 10.1016/j.whi.2020.07.001. Epub 2020 Aug 12. PMID: 32798085.
[59] *Id.*

affect who is able to be with them before and after an abortion, e.g., if their preferred companion is unable to travel to be with them where they now must go to obtain an abortion); and heightened health risks. Though the major-complication rate for abortion remains low throughout pregnancy, the risks do increase as a pregnancy progress.[60]

59. These issues may also impose costs on the people who own, operate, and work for businesses that provide abortion care because they restrict their ability to provide care to people in a manner that is consistent with medical judgment about what is the most appropriate method for providing the health care sought. People who work in health care—and other jobs involving the care of others—frequently report that they do so because it is fulfilling to help other people.[61] It is also important to note that "burnout" (e.g., due to a stressful work environment or inadequate staffing)[62] is frequently cited among those who stop working for health care providers, and heightened stress may occur when abortion providers are operating at their full capacity and trying to expand that capacity, or when they are otherwise forced to provide health care in a manner that does not align with their patients' needs and preferences. Moreover, for some providers and clinics who only offer medication abortion, eliminating medication abortion would eliminate their ability to provide abortions altogether.

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[60] Ushma D. Upadhyay et al., *Incidence of Emergency Department Visits and Complications After Abortion*, 125 OBSTETRICS & GYNECOLOGY 175, 181 (2015).

[61] See, e.g., Salyers MP, Rollins AL, Kelly YF, Lysaker PH, Williams JR. Job satisfaction and burnout among VA and community mental health workers. Adm Policy Ment Health. 2013 Mar;40(2):69-75. doi: 10.1007/s10488-011-0375-7. PMID: 21972060; PMCID: PMC3980458.

[62] See, e.g., Shah MK, Gandrakota N, Cimiotti JP, Ghose N, Moore M, Ali MK. Prevalence of and Factors Associated With Nurse Burnout in the US. *JAMA Netw Open.* 2021;4(2):e2036469. doi:10.1001/jamanetworkopen.2020.36469.

IV.C. Effects of Not Being Able to Control the Timing and/or Number of Children Due to Restricted Abortion Access

60. As described above, ceasing to allow medication abortion is likely to prevent some people from obtaining abortions, both people who would prefer a medication abortion and people who would prefer a surgical abortion. This means having a child earlier than they otherwise would and/or having more children than they otherwise would. Each possible outcome involves substantial costs.

61. It is well established that continuing a pregnancy to childbirth poses greater short-term health risks than having an abortion.[63] There is also evidence that restricted abortion access increases violence against women, [64] which is consistent with surveys in which respondents indicate "having an abusive partner" as a reason for seeking an abortion.[65]

62. In terms of the overall economic costs of having a child, some costs are obvious because they involve monetary expenditures, and some are less obvious because they involve lost earnings or impaired earnings potential due to the fact that having a child may mean a person has fewer hours available to work and/or earn income.

63. Expenditures associated with pregnancy and delivery can include medical costs for some individuals (e.g., those who are uninsured) that can be substantial. Other costs besides direct medical expenses include transportation costs and childcare costs associated with medical care and other activities typically done in advance of having a child (such as parenting classes

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[63] Elizabeth G. Raymond & David A. Grimes, *The Comparative Safety of Legal Induced Abortion and Childbirth in the United States*, 119 OBSTETRICS & GYNECOLOGY 215, 216–17 (2012).
[64] Sarah C. M. Roberts, M. Antonia Biggs, Karuna S. Chibber *et al., Risk of violence from the man involved in the pregnancy after receiving or being denied an abortion*, 12 BMC MED. 144 (2014); Caterina Muratori, *The Impact of Abortion Access on Violence Against Women*, (Department of Economics, University of Reading, Working Paper No. 2021-03, 2021).
[65] *See, e.g.*, Karuna S. Chibber, M Antonia Biggs, Sarah C. M. Roberts & Diana Greene Foster, *The role of intimate partners in women's reasons for seeking abortion*, WOMENS HEALTH ISSUES, (2014); M Antonia Biggs, H. Gould & Diana Greene Foster, *Understanding why women seek abortions in the US*, 13 BMC WOMEN'S HEALTH 29 (2013).

and purchasing equipment/materials that are necessary for the child's wellbeing and safety). These costs—particularly at a time when a new member is being added to the household—can push individuals further into poverty.

64. Child-*rearing* expenses include housing, food, transportation, clothing, health care, childcare, and many miscellaneous expenses. These costs typically exceed $9,000 annually, even for low- and middle-income households.[66] As I described above, a substantial share of individuals seeking abortion are already in poverty. Adding a child to such a household without substantially expanding their resources will thrust such an individual deeper into poverty. Given the highly persistent nature of economic circumstances, this is likely to affect the individual for their entire life.

65. In addition, time-costs associated with pregnancy, childbearing, and childrearing can make it difficult for people to continue in school, to make other investments in their careers, to work as many hours as they would like, to maintain jobs, to look for work, etc. Any of these things can deplete an individual's financial resources in the short run and in the long run.

66. In sum, monetary costs and time-costs (associated with pregnancy, childbearing, and childrearing), are so substantial that they could cause significant and persistent economic harm by putting an individual on an entirely different life course in which they have more limited resources (possibly on top of having another child to provide for).

67. Many carefully designed studies have quantified such effects using different approaches to data analysis, using different data sets, etc. and examining different contexts, different populations, and different outcomes.[67]

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[66] Mark Lino et al. "Expenditures on Children by Families, 2015" UNITED STATES DEPARTMENT OF AGRICULTURE, CENTER FOR NUTRITION POLICY AND PROMOTION MISCELLANEOUS REPORT NO. 1528-2015 (2017).

[67] For studies documenting effects on economic outcomes, *see, e.g.*, Aguero, Jorge M., and Mindy S. Marks, 2008 "Motherhood and Female Labor Force Participation: Evidence from Infertility Shocks." The American Economic

68. One such study, which used cutting-edge methods for estimating causal effects to estimate the effects on economic outcomes, found that being denied an abortion increased financial distress in all five years of their five-year follow-up period.[68] The analyses aimed at better understanding this effect on financial distress indicated that being denied an abortion increased a person's amount of past-due debt by an average of $1,750, increased the number of negative public records on their credit reports (such as bankruptcy, evictions, and tax liens) by 81 percent, and reduced their income by 6 percent.[69]

69. Researchers have also examined how state policy changes altering abortion access affected the socioeconomic outcomes for the general population of women in the state, which can be measured using very large data sets. Studies examining the effects of bans on abortion show deleterious effects on residents' educational attainment and economic outcomes (including employment, earnings, family income, poverty, and public assistance receipt), particularly among Black women.[70] Along similar lines, research on the effects of impaired access to abortion resulting from state targeted-regulations on abortion providers ("TRAP Laws") also show deleterious effects on educational attainment, particularly among Black women.[71]

70. To put the estimated effects on educational attainment into context, it is important

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Review, 98(2): 500-504; Adda, Jerome, Christian Dustmann, and Katrien Stevens, 2017, "The Career Costs of Children," *Journal of Political Economy*, 125(2): 293-337; Kleven, Henrik, Camille Landais, and Jakob Egholt Sogaard. 2019, "Children and Gender Inequality: Evidence from Denmark," *American Economic Journal: Applied Economics*, 11(4): 181-209; Sandler, Danielle, and Nichole Szembrot, 2019, "Maternal Labor Dynamics: Participation, Earnings, and Employer Changes," U.S. Census Bureau Center for Economic Studies Working Paper No. CES 19-33, Washington, DC.

[68] Sarah Miller et. al., *Economic Consequences of Being Denied an Abortion*, Am. ECON. J.: ECON. POL'Y, (Forthcoming) 1, 5 (2021).

[69] *Id.* at 4.

[70] Joshua D. Angrist & William N. Evans, *Schooling and Labor Market Consequences of the 1970 State Abortion Reforms*, 18 RSCH. IN LAB. ECON. 75, 75-113 (2000); Jason M. Lindo et al., *Legal Access to Reproductive Control Technology, Women's Education, and Earnings Approaching Retirement*, 110 AEA PAPERS & PROC. 231, 234 (2020); Kelly Jones, *At a Crossroads: The Impact of Abortion Access on Future Economic Outcomes*, (Am. Univ., Working Paper No. 2021-02, 2021), https://doi.org/10.17606/0Q51-0R11.

[71] *Id.*

to keep in mind that the benefits of education are likely to go well beyond wages. As Oreopolous and Salvanes write in their summary of the literature on the non-pecuniary benefits of education: "Gains from school occur from being in a job that not only pays more but also offers more opportunities for self-accomplishment, social interaction, and independence. Schooling generates occupational prestige. It reduces the chance of ending up on welfare or unemployed. It improves success in the labor market and the marriage market. Better decision-making skills learned in school also lead to better health, happier marriages, and more successful children. School also leads to better health, happier marriages, and more successful children. Schooling also encourages patience and long-term thinking. Teen fertility, criminal activity, and other risky behaviors decrease with it. Schooling promotes trust and civic participation. It teaches students how to enjoy a good book and manage money. And for many, schooling has consumption value too."[72]

71. As noted above, a majority of those obtaining abortions have previously given birth, and people seeking abortions often report that they are doing so out of concern for their existing children. In addition, many individuals will go on to have children later in their lives after they have had an abortion. As such, the lives of these children will also be altered by the impacts on their parents described above.

72. More limited economic resources can result in detrimental effects on children's behavioral and emotional issues,[73] and on test scores,[74] which can lead to grade repetition.

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[72] Philip Oreopoulos & Kjell G. Salvanes, *Priceless: The Nonpecuniary Benefits of Schooling*, 25 J. OF ECON. PERSP. 159, 159-84 (2011).

[73] *See, e.g.*, Randall Akee, William Copeland, E. Jane Costello, & Emilia Simeonova, *How Does Household Income Affect Child Personality Traits and Behaviors?*, 108 AM. ECON. REV. 775, 775-827 (2018); Kevin Milligan & Mark Stabile, *Do Child Tax Benefits Affect the Well-Being of Children? Evidence from Canadian Child Benefit Expansions*, 3 AM. ECON. J.: ECON. POL'Y 175, 175–205 (2011).

[74] *See, e.g.*, Sandra E. Black, Paul J. Devereux, Katrine V. Løken & Kjell G. Salvanes, *Care or Cash? The Effect of Child Care Subsidies on Student Performance*, 96 REV. OF ECON. AND STAT. 824, 824–37 (2014); Gordon B. Dahl & Lance Lochner, *The Impact of Family Income on Child Achievement: Evidence from the Earned Income Tax Credit*,

Economic circumstances during childhood also have long-run effects which show up in educational attainment and adult earnings,[75] as well as measures of earnings capacity, economic self-sufficiency, neighborhood quality, and life expectancy.[76] Along similar lines, parental education affects children's health at birth,[77] cognitive skills and behavioral problems in childhood,[78] the probability of repeating a grade,[79] and involvement in crime.[80]

IV.D. Effects on Society More Broadly

73. The issues described above, which would result from eliminating access to medication abortion, pertain to the lives of the individuals seeking abortion, their families, *and the broader public*.

74. Among the issues not touched on above, it bears mentioning that any decision that reduces access to medication abortion, and ultimately denies abortions to individuals who want them, will generally increase health care costs via the costs of health care during pregnancy, childbearing, and beyond. All of these costs can be extremely high, particularly when health complications arise.

75. Health care costs are a societal issue because of many unique features of the industry, including health insurance. For private insurance, rates are set according to the costs

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102 AM. ECON. REV. 1927, 1927–56 (2012); Kevin Milligan, & Mark Stabile, *Do Child Tax Benefits Affect the Well-Being of Children? Evidence from Canadian Child Benefit Expansions*, 3 AM. ECON. J.: ECON. POL'Y 175, 175–205 (2011).

[75] Andrew Barr, Jonathan Eggleston & Alexander A. Smith, *Investing in Infants: The Lasting Effects of Cash Transfers to New Families*, THE Q. J. OF ECON., (2022).

[76] Martha J. Bailey, Hilary Hoynes, Maya Rossin-Slater & Reed Walker, *Is the Social Safety Net a Long-Term Investment? Large-Scale Evidence from the Food Stamps Program*, (Nat'l Bureau of Econ. Rsch., Working Paper No. 26942, 2020).

[77] Janet Currie & Enrico Moretti, *Mother's Education and the Intergenerational Transmission of Human Capital: Evidence from College Openings*, 118 Q. J. OF Econ. 1495, 1495–532 (2003).

[78] Pedro Carneiro, Costas Meghir & Matthias Parey, *Maternal Education, Home Environments, and the Development of Children and Adolescents*, 11 J. OF THE EUR. ECON. ASS'N 123,123-60 (2013).

[79] Philip Oreopoulos, Marianne E. Page & Ann Huff Stevens, *The Intergenerational Effects of Compulsory Schooling*, 24 J. OF LABOR ECON. 729, 729-60 (2006).

[80] Aaron Chalfin & Monica Deza, *The intergenerational effects of education on delinquency*, 159 J. OF ECON. BEHAV. & ORG. 553, 553-71, (2019).

associated with the set of individuals who are being insured (i.e., the risk pool). Thus, if the costs increase for any subset of those individuals (e.g., those being delayed or prevented from obtaining an abortion legally), it increases the rate for *everyone* being insured.

76. Similarly, a (much) broader set of individuals is affected by increases in health care costs for individuals on public health insurance. In that regard, increases in health care costs (e.g., from individuals being delayed or prevented from obtaining an abortion legally) will increase the costs imposed on taxpayers.

77. It is worth noting here that the number of people on public health insurance is likely to increase if medication abortion is no longer available as a result of the economic effects described above, which will additionally affect taxpayers. Those economic effects will also affect taxpayers by increasing the need for other public assistance and social safety net programs (including food stamps, housing assistance, tax credits, and other programs and services).

78. Moreover, the effects on people seeking abortion and on their children are likely to affect many other people's lives in many other ways.[81] A rich literature shows that people have significant impacts on the lives of others through family and friendship networks, neighborhoods, schools, and many other channels. Moreover, it is clear from this literature that the effect of poverty—which will be increased if medication abortion ceases to be available—is pervasive.

79. Further, researchers talk about "poverty traps" because it is so difficult to escape poverty[82] and "intergenerational poverty" because of the high degree to which poverty persists

[81] See, e.g., Diana Greene Foster, *The Turnaway Study: Ten Years, a Thousand Women, and the Consequences of Having—or Being Denied—an Abortion* (2020).
[82] See, e.g., Bowles, Samuel, Durlauf, Steven N. and Hoff, Karla. *Poverty Traps*, Princeton: Princeton University Press, 2006. https://doi.org/10.1515/9781400841295.

from one generation to the next.[84] Research on these topics indicates that effects on poverty can be expected to last throughout individuals' lives and into subsequent generations.

80. For all of these reasons, eliminating access to medication abortion will impose severe costs on many individuals and society as a whole, both in the short term and for future generations, as well as healthcare delivery systems across the country.

Executed January 13, 2023

Jason Lindo

Jason Lindo, Ph.D.

[84] See, e.g., Harper, Caroline, Rachel Marcus, and Karen Moore. "Enduring Poverty and the Conditions of Childhood: Lifecourse and Intergenerational Poverty Transmissions." *World Development* 31, 2003.

EXHIBIT A

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CURRENT POSITIONS

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Research Fellow, Institute for the Study of Labor (IZA), 2010–Present
Co-Editor, *Economic Inquiry*, 2016–Present

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Associate Editor, *Journal of Population Economics*, 2016–2022
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Visiting Research Scholar, Montana State University, 2016 – 2020
Associate Professor of Economics, Texas A&M University, 2013–2018
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Assistant Professor of Economics, University of Oregon, 2009–2013

EDUCATION

Ph.D., Economics, University of California, Davis, 2009
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RESEARCH INTERESTS

reproductive health, health behaviors and outcomes, employment shocks and family dynamics, youth, crime

TEACHING INTERESTS

Econometric/Empirical Methods; Health (Care, Behavior, Outcomes); Labor; Gender; Demography

PUBLICATIONS

Peer-Reviewed Publications

Lindo, Jason M., Isaac D. Swensen, and Glen R. Waddell. **"Effects of Violent Media Content: Evidence from the Rise of the UFC,"** *Journal of Health Economics*, forthcoming.

Lindo, Jason M. ⓡ Mayra Pineda-Torres. **"New Evidence on The Effects of Mandatory Delay Laws for Abortion,"** *Journal of Health Economics*, 80, 2021.

Kelly, Andrea, Jason M. Lindo, and Analisa Packham. **"The Power of the IUD: Effects of Expanding Access to Contraception Through Title X Clinics,"** *Journal of Public Economics*, 192, 2020.

Lindo, Jason M., Caitlin Myers, Andrea Schlosser, and Scott Cunningham. **"How Far is Too Far? New Evidence on Abortion Clinic Closures, Access, and Abortions,"** *The Journal of Human Resources*, 55(4), pp. 1137-1160, 2020.

Lindo, Jason M. **"Weighing the Evidence on the Likely Effects of Expanding Access to LARCs on Poverty,"** *American Journal of Obstetrics & Gynecology*, 222(4), pp. S864-S865, 2020.

Lindo, Jason M., Dave Marcotte, Isaac D. Swensen, and Jane Palmer. **"Any Press is Good Press? The Unanticipated Effects of Title IX Investigations on University Outcomes,"** *Economics of Education Review*, 73, 2019.

Lindo, Jason M., Jessamyn Schaller, and Benjamin Hansen. **"Caution! Men Not At Work: Gender Specific Labor Market Conditions and Child Maltreatment,"** *Journal of Public Economics*, 163, pp. 77-98, 2018.

Lindo, Jason M. and María Padilla-Romo. **"Kingpin Approaches to Fighting Crime and Violence: Evidence from Mexico's Drug War,"** *Journal of Health Economics*, 58, pp. 253-268, 2018.

Bondurant, Samuel, Jason M. Lindo, and Isaac D. Swensen. **"Substance Abuse Treatment Centers and Local Crime,"** *Journal of Urban Economics*, 104, pp. 124-133, 2018.

Lindo, Jason M., Peter Siminski, and Isaac D. Swensen. **"College Party Culture and Sexual Assault,"** *American Economic Journal: Applied Economics*, 10(1), pp. 236-65, 2018.

Lindo, Jason M. and Analisa Packham. **"How Much Can Expanding Access to Long-Acting Reversible Contraceptives Reduce Teen Birth Rates?"** *American Economic Journal: Economic Policy*, 9(3), pp. 348-76, 2017.

Barreca, Alan I., Jason M. Lindo, and Glen R. Waddell. **"Heaping-Induced Bias in Regression-Discontinuity Designs,"** *Economic Inquiry*, 54(1), pp. 268–293, 2016.

Lindo, Jason M., Peter Siminski, and Oleg Yerokhin. **"Breaking the Link Between Legal Access to Alcohol and Motor Vehicle Accidents: Evidence from New South Wales,"** *Health Economics*, 25(7), pp. 908–928, 2015.

Lindo, Jason M. **"Aggregation and the Estimated Effects of Economic Conditions on Health,"** *Journal of Health Economics*, 40, pp. 83–96, 2015.

Lindo, Jason M. and Charles Stoecker. **"Drawn into Violence: Evidence on 'What Makes a Criminal' from the Vietnam Draft Lotteries,"** *Economic Inquiry*, 52(1), pp.239–258, 2014.

Lindo, Jason M., Isaac D. Swensen, and Glen R. Waddell. **"Alcohol and Student Performance: Estimating the Effect of Legal Access,"** *Journal of Health Economics*, 32(1), pp. 22–32, 2013.

Lindo, Jason M., Isaac D. Swensen, and Glen R. Waddell. **"Are Big-Time Sports a Threat to Student Achievement?"** *American Economic Journal: Applied Economics*, 4(4), pp. 254–274, 2012.

Cuffe, Harold, William T. Harbaugh, Jason M. Lindo, Giancarlo Musto, and Glen R. Waddell. **"Evidence on the Efficacy of School-Based Incentives for Healthy Living,"** *Economics of Education Review*, 31(6), pp. 1028–1036, 2012.

Barreca, Alan I., Melanie Guldi, Jason M. Lindo, and Glen R. Waddell. **"Saving Babies? Revisiting the Effect of Very Low Birth Weight Classification,"** *The Quarterly Journal of Economics*, 126(4), pp. 2117–2123, 2011.

Lindo, Jason M. **"Parental Job Loss and Infant Health,"** *Journal of Health Economics*, 30(5), pp. 869–879, 2011.

Lindo, Jason M., Nicholas J. Sanders, and Philip Oreopoulos. **"Ability, Gender, and Performance Standards: Evidence from Academic Probation,"** *American Economic Journal: Applied Economics*, 2(2), pp. 95–117, 2010.

Lindo, Jason M. **"Are Children Really Inferior Goods? Evidence from Displacement-driven Income Shocks,"** *The Journal of Human Resources*, 45(2), pp. 301-327, 2010.

Book Chapters and Other Academic Publications

Bullinger, Lindsey Rose, Jason M. Lindo, and Jessamyn Schaller. **"Economic Determinants of Child Maltreatment,"** in Alain Marciano and Giovanni Battista Ramello, eds., *Encyclopedia of Law and Economics, Second Edition*, 2021.

Lindo, Jason M., Mayra Pineda-Torres, David Pritchard, and Hedieh Tajali. **"Legal Access to Reproductive Control Technology, Women's Education, and Earnings Approaching Retirement,"** *AEA Papers and Proceedings*, 110, pp. 231-235, 2020.

Bailey, Martha J. and Jason M. Lindo. **"Access and Use of Contraceptives and Its Effects on Women's Outcomes in the United States,"** in Susan L. Averett, Laura M. Argys, and Saul D. Hoffman, ed., *Oxford Handbook on the Economics of Women*, New York: Oxford University Press, 2018.

Lindo, Jason M. and Jessamyn Schaller. **"Economic Determinants of Child Maltreatment,"** in Jürgen Back-

haus, ed., *Encyclopedia of Law and Economics*, pp. 1–10, NY: Springer, 2014.

Lindo, Jason M. and Peter Siminski. **"Should The Legal Age For Buying Alcohol Be Raised to 21 Years?"** *Medical Journal of Australia*, 201(10), p. 571, 2014.

Page, Marianne, Ann Huff Stevens, and Jason M. Lindo. **"Parental Income Shocks and Outcomes of Disadvantaged Youth in the United States,"** in Jonathan Gruber, ed., *An Economic Perspective on the Problems of Disadvantaged Youth*, pp. 213–235, Chicago: University of Chicago Press, 2009.

Policy Briefs and Editorials

Jason M. Lindo, Krishna Regmi, and Isaac D. Swensen, **"Layoffs, Divorce, and the Effect of Unemployment Insurance"** *EconoFact*, October 21, 2020.

Andrea M. Kelly, Jason M. Lindo, and Analisa Packham, **"Could Expanding Access to Contraception Improve Economic Outcomes?"** *EconoFact*, August 20, 2019. Republished by *PBS News Hour*, August 29, 2019.

Jason M. Lindo, Peter Siminski, and Isaac D. Swensen, **"Big game days in college football linked with sexual assault,"** *The Conversation*, September 20, 2018.

Jason M. Lindo, Dave E. Marcotte, Jane E. Palmer, and Isaac D. Swensen, **"Any Press is Good Press? Study Finds Federal Investigations of University Responses to Sexual Misconduct Cases May Help Enrollments,"** *ProMarket: The Blog of the Stigler Center at the University of Chicago Booth School of Business*, August 16, 2018.

Jason M. Lindo, Peter Siminski, and Isaac D. Swensen, **"Football, College Party Culture, and Sexual Assault,"** *EconoFact*, July 19, 2018.

Bondurant, Samuel, Jason M. Lindo, and Isaac D. Swensen, **"Access to Substance Abuse Treatment, Drug Overdose Deaths, and Crime,"** *EconoFact*, March 16, 2018.

Lindo, Jason M. **"Defunding Planned Parenthood Didn't Reduce the Number of Abortions in Texas,"** *Dallas Morning News*, July 6, 2017.

Lindo, Jason M. and Analisa Packham. **"Lowering the Teenage Birthrate,"** *New York Times*, July 13, 2015.

Lindo, Jason M. and Analisa Packham. **"Long-acting Reversible Contraceptives Reduced Teen Pregnancies, Especially in Higher-Poverty Areas,"** *UC Davis Center for Poverty Research Policy Brief*, 4(3), 2015.

Lindo, Jason M. and María Padilla-Romo. **"Kingpin Approaches to Fighting Crime and Violence: Evidence from Mexico's Drug War,"** *Cato Research Briefs in Economic Policy*, No. 31, July 2015.

Lindo, Jason M. **"Gender-Specific Measures of Economic Conditions and Child Abuse,"** *Center for the Study of Women in Society Research Matters*, Spring 2013.

Working Papers

Lindo, Jason M., Krishna Regmi, and Isaac Swensen. **"Stable Income, Stable Family,"** NBER Working Paper No. 26228.

Cao, Andy, Jason M. Lindo, and Jiee Zhong. **"Can Social Media Rhetoric Incite Hate Incidents? Evidence from Trump's "Chinese Virus" Tweets,"** NBER Working Paper No. 30588.

GRANTS AND COMPETITIVE EXTERNAL FELLOWSHIPS

Laura and John Arnold Foundation, PI, 2018 ($66,710)

National Institute for Health Care Management Research and Education Foundation, PI, 2017

Turnovsky Fellowship, 2017

US Department of Justice Research Grant, Co-PI with Isaac D. Swensen, Award 2014-R2-CX-0015, 2014

INTERNAL GRANTS

Texas Census Research Data Center Proposal Development Grant, 2014

Texas Census Research Data Center Proposal Development Grant, 2013

Center for the Study of Women in Society Faculty Research Grant, University of Oregon, 2012

Junior Professorship Development Grant, University of Oregon, College of Arts and Sciences, 2011
Junior Professorship Development Grant, University of Oregon, College of Arts and Sciences, 2010
Junior Faculty Award, University of Oregon, 2009
Graduate Student Travel Award, UC Davis, 2007

HONORS AND AWARDS

Best Supporter of Graduate Students, Texas A&M Department of Economics, 2020
Outstanding Graduate Instructor of the Year, Texas A&M Department of Economics, 2018
Best Graduate Advisor, Texas A&M Department of Economics, 2017
Outstanding Graduate Instructor of the Year, Texas A&M Department of Economics, 2013
Emerging Scholar, Center for Poverty Research, University of Kentucky, 2011
Phi Beta Kappa, 2005

INVITED PRESENTATIONS AND WORKSHOPS

2022–2023 (including planned): Texas A&M University (Dept of History's roundtable about Dobbs v. Jackson Women's Health Organization), Economists' Perspectives on Abortion Access (American Society of Health Economists' Special Event), Vanderbilt Law School Law and Economics Workshop

2021–2022: Elon University, University of Connecticut, Essen Health Conference (keynote)

2020–2021: Centre for Health Economics–Monash Business School, Monash University Department of Economics, Association for Mentoring & Inclusion in Economics (AMIE)

2019–2020: Miami University, Indiana University, San Diego State University, Society of Family Planning Annual Meeting, American Economic Association Annual Meetings, University of Michigan, University of South Florida

2018–2019: 3rd IZA Workshop on Gender and Family Economics, University of California at Davis, Brookings Conference on Improving Opportunity Through Family Planning

2017–2018: University of Kansas, Stata Texas Empirical Micro Conference, Sam Houston State University, Ifo Institute Workshop on Economic Uncertainty and the Family, 18th Annual Southeastern Health Economics Study Group, University of Tennessee, Texas A&M University (Agricultural Economics), Birdsall House Conference on Women (Center for Global Development), Texas A&M University (School of Public Health), University of South Carolina, Columbia University, American University, NBER Health Economics Program Meetings, University of California at Davis, Montana State University Initiative for Regulation and Applied Economic Analysis Conference on "Economics of Reproductive Health Policies"

2016–2017: Montana State University, University of Colorado at Boulder, West Virginia University, Fall Meetings of the Association for Public Policy Analysis & Management, Annual Meetings of the American Economics Association, University of California at Merced, Southern Methodist University, Victoria University of Wellington

2015–2016: Texas Tech University, Southern Economic Association Annual Meetings, National Institute for Health Care Management Webinar on Adolescent Health and Teen Pregnancy, NBER Children's Program Meetings, China Meeting of the Econometric Society

2014–2015: Monash University, University of North Carolina at Charlotte, Baylor University, SOLE/EALE World Meetings

2013–2014: Tulane University, University of Texas at Dallas, Dalhousie University, University of Houston and Rice University, University of Wollongong, Victoria University of Wellington, Massey University

2012–2013: Labour Econometrics Workshop (Discussant), University of Wollongong, Texas A&M University, University of Illinois at Urbana-Champaign, Louisiana State University, Michigan State University, University of California at Merced, 5th Annual Meeting on the Economics of Risky Behaviors, NBER Children's Program Meetings

2011–2012: The Australian National University, University of Wollongong, Australian Labour Econometrics Workshop, University of Notre Dame, Case Western Reserve University, University of Maryland, University of Oregon,

SOLE Annual Meetings, IZA/SOLE Transatlantic Meeting of Labor Economists

2010–2011: NBER Children's Program Meetings, SOLE Annual Meetings, Public Policy and the Economics of the Family Conference at Mount Holyoke College, University of Kentucky, Portland State University

2009–2010: Western Economic Association Annual Meetings, American Economic Association Annual Meetings (Discussant), SOLE/EALE World Meetings, The Economics of Family Policy Conference at the University of Bergen, NBER Children's Program Meetings, Economic Demography Workshop, University of British Columbia

2008–2009: NBER Higher Education Program Meetings, RAND Corporation, University of Colorado at Denver, Stanford Institute for Economic Policy Research, University of Oregon, The College of William and Mary, Sonoma State University, California State University at Sacramento, All UC Labor Conference, UC Davis Economy, Justice, and Society Retreat, Western Economic Association Annual Meetings

ADDITIONAL PROFESSIONAL ACTIVITIES

Co-Director of Mentoring: Association for Mentoring & Inclusion in Economics (AMIE), 2021–Present

Referee: *American Economic Journal: Applied Economics, American Economic Journal: Economic Policy, American Economic Review, American Journal of Health Economics, American Journal of Obstetrics and Gynecology, The B.E. Journal of Economic Analysis and Policy, Children and Youth Services Review, Contemporary Economic Policy, Contraception, Demography, Eastern Economic Journal, The Economic Journal, Economics of Education Review, Economic Inquiry, Education Evaluation and Policy Analysis, Empirical Economics, Health Economics, Industrial and Labor Relations Review, Institute for Women's Policy Research, Journal of Applied Econometrics, Journal of Econometrics, Journal of Family and Economic Issues, Journal of Health Economics, The Journal of Human Resources, Journal of The Japanese and International Economies, Journal of Labor Economics, Journal of Labor Research, Journal of Law Economics and Organization, Journal of Policy Analysis and Management, Journal of Political Economy, Journal of Population Economics, Journal of Public Economics, Journal of the Royal Statistical Society, Labour Economics, Proceedings of the National Academy of Sciences, Public Choice, The Quarterly Journal of Economics, Review of Economics of The Household, Review of Economic Studies, The Southern Economic Journal, Women's Health Issues*

Reviewer: National Science Foundation, APPAM Program Committee

Co-organizer or Committee Member: Montana State University Initiative for Regulation and Applied Economic Analysis Conference on "Economics of Unemployment Insurance" 2020 (Co-organizer), Texas Health Economics Workshop 2019 (Co-organizer), Montana State University Initiative for Regulation and Applied Economic Analysis Conference on "Economics of Reproductive Health Policies" 2018 (Co-organizer), Annual Health Economics Conference 2018 (Committee Member), Economic Demography Workshop 2018 (Committee Member), Midwestern Econometrics Group Meetings 2017 ((Committee Member), Economic Demography Workshop 2017 (Committee Member), 15th Annual Labour Econometrics Workshop 2012 (Committee Member)

Advisory Board Member: Michigan Contraceptive Access, Research, and Evaluation Study, 2018–Present

TEACHING EXPERIENCE

Texas A&M University

Introduction to Economic Data Analysis (planned Spr 23)

Program/Policy Evaluation (Fall 14, Spr 14, Spr 16, Spr 17, Spr 18, Fall 19, Fall 20, Spr 21, Spr 22, planned Spr 23)

PhD-level Econometrics (Fall 13, Fall 14, Spr 15, Spr 16, Spr 17, Spr 18, Spr 19, Spr 21, Spr 22)

Shanghai University of Finance and Economics

Short Course in Econometric Methods for Causal Inference (Summer 16)

University of Oregon

Graduate Labor Economics (Winter 10, Fall 10, Spr 13)

Topics in Labor Economics (Fall 09, Winter 10, Fall 10, Spr 11, Fall 11, Spr 12, Spr 13)

Economics of Gender (Spr 11, Fall 11, Spr 12)

PHD STUDENT ADVISING (including graduation year and initial placement)

Texas A&M University

Jing Zhang (in progress)
Maxwell Bullard (co-chair, in progress)
Jiee Zhong (co-chair, in progress)
Wesley Miller (in progress)
Andre'nay Harris (in progress)
Mayra Pineda Torres (chair, 2022), Georgia Tech University
David Pritchard (chair, 2022), U.S. Census Bureau
Hedieh Tajali (2022), University of Edinburgh
Andrea Kelly (chair, 2020), Grinnell College
Manuel Hoffman (2020), University of Heidelberg
Joshua Witter (2020), Correlation Research Division at the Church of Jesus Christ of Latter-Day Saints
Roberto Mosquera (co-chair, 2019), Universidad de las Américas
Brittany Street (2019), University of Missouri
John Anders (2019), US Census Bureau
Ruichao Si (2019), Nankai University
Samuel Bondurant (chair, 2018) US Census Bureau
Abigail Peralta (2018), Louisiana State University
Yongzhi Sun (2018), Southwestern University of Finance and Economics
María Padilla-Romo (chair, 2017), University of Tennessee
Emily Zheng (chair, 2017), Chinese University of Hong Kong - Shenzen
Jaegum Lim (2017), Korean National Assembly
Analisa Packham (chair, 2016), Miami University
Pierre Mouganie (2015), American University of Beirut
Jillian Carr (2015), Purdue University

University of Oregon

Kristian Holden (co-chair, 2014), American Institutes for Research (AIR)
Harold Cuffe (co-chair, 2013), Victoria University of Wellington
Isaac Swensen (co-chair, 2013), Montana State University
Brian Vander Naald (2012), University of Alaska, Juneau
Eric Duquette (2010), Economic Research Service, USDA

UNIVERSITY SERVICE

Faculty Senate, 2014-2016
Climate and Diversity Committee, 2015-2016
Academic Affairs Committee, 2014-2015

DEPARTMENTAL SERVICE

Texas A&M University

Graduate Instruction Committee, 2021–2022
Junior Faculty Mentor, 2021–2022
Econometrics Search Committee, 2019–2021
Economics Department Head Search Committee, 2019–2020
PERC Applied Microeconomics Workshop Co-organizer, 2019–2020

Organizer, Inaugural Public Labor and Industrial Organization (PLIO) Alumni Conference, 2019
Graduate Placement Co-director, 2013–2014, 2015-2016, 2017–2018, 2018–2019
Economics Undergraduate Research Opportunities Program Advisor, 2014–2015, 2018–2019
Executive Committee, 2017–2018
Graduate Instruction Committee, 2017–2018
Applied Microeconomics Search Committee Chair, 2014–2015
Applied Microeconomics Search Committee, 2013–2014

University of Oregon

McNair Scholar Advisor, 2012–2013
Graduate Placement Co-director, 2010–2012
Undergraduate Program Committee, 2009–2013
Seminar Committee, 2009–2010
Applied Microeconomics Brownbag Co-organizer, 2009–2010

SELECTED MEDIA APPEARANCES AND COVERAGE

Television:

"Economists warn about effects of abortion restrictions," Spectrum News 1, 5/19/22
"Rape on College Campuses," Not Safe with Nikki Glaser (Comedy Central), 7/12/16
"College Football and Campus Sexual Assault," Outside The Lines (ESPN), 2/19/16
"College Game Day's Disturbing Trend," Watching the Hawks (RT), 1/11/16

Radio/Podcast:

"With Roe v. Wade overturned, economic disparities are poised to get worse," Marketplace, 6/24/22
"Women who are denied abortions risk falling deeper into poverty," Morning Edition (NPR), 5/26/22
"Episode 33: Persistent Effects of Violent Media Content," Probable Causation, 8/4/20
"Persistent Effects of Violent Media Content," Vox's The Weeds, 5/26/20 (46th minute)
"The benefits of IUDs," Vox's The Weeds, 3/26/19 (37th minute)
"What happens when abortion providers shut down," Vox's The Weeds, 5/3/17 (50th minute)
"Is There a Connection Between Football Games and Risks For Rape?" Morning Edition (NPR), 2/17/16

Print:

"Update: Judge has ruled abortions can continue in Kentucky for now," ABC 36, 7/22/22
"Roe Stood for 49 Years. It Revolutionized Life for Women," 6/24/22, Wired
"Study Finds Reduced Involvement In Violent Crime For UFC Viewers," 5/20/22, MMA News
"5 ways abortion bans could hurt women in the workforce," 5/19/22, Vox
"UFC mixed martial arts fighting events appear to reduce involvement in violent crime," 5/18/22, PsyPost
"Limiting abortion access is bad for the economy," 5/16/22, CNN
"When SafeGraph pulled abortion clinic data..." 5/13/22, Protocol
"Sensemaker: Who abortion bans hurt," 5/12/22, Tortoise Media
"Roe v. Wade isn't just about women's rights. The economic implications..." 5/7/22, Business Insider
"Abortion Rollback Risks Erasing Decades of Economic Gains for U.S. Women," 5/4/22, Bloomberg
"Being Denied an Abortion Has Lasting Impacts on Health and Finances," 12/22/21, Scientific American
"Texas abortion ban is an early glimpse of what post-Roe America would look like for women," 5/18/21, CNN
"Where Abortion Access Would Decline if Roe v. Wade Were Overturned," 5/18/21, The New York Times
"What History Says Will Happen Next in Iran," 1/7/20, The Atlantic
"How To Reduce Abortion," 10/17/19, New York Times

"Why America's Abortion Rate Might Be Higher Than It Appears," 9/20/19, New York Times
"Tennessee's abortion wait period law faces court arguments," 9/20/19, Associated Press (reprinted worldwide)
"Mandatory waiting periods can make abortions nearly $1,000 more expensive," 9/10/19, MarketWatch
"Could expanding access to contraception improve economic outcomes?" 8/29/19, PBS News Hour
"Judge blocks new Arkansas abortion laws just before midnight," 7/24/19, Arkansas Democrat Gazette
"Where Roe v. Wade Has the Biggest Effect," 7/18/19, New York Times
"Former Gov. Hickenlooper unveils plan to expand access to women's contraception," 5/29/19, ABC News
"Colorado teen pregnancies dropped 20% near these clinics...funding is at risk," 3/22/19, Denver Post
"Better access to IUDs drove a 20% drop in teen pregnancy and abortions, report finds," 3/18/19, Daily Mail
"One Abortion Clinic Remains Open In Missouri, Following New State Requirements," 10/3/18, NPR
"Do campus rape investigations damage colleges? Actually, the opposite may be true," 7/25/18, Salon
"Study finds home football games elevate cases of sexual assault" 2/1/18, The Battalion.
"Abortion Clinics in Texas Haven't Reopened, and It's Causing Real Damage to Real Women," 5/3/17, Salon
"The IUD Revolution," 3/23/16, Vox
"Will Nabbing of 'El Chapo' Actually Help Mexico Win the War on Drugs?" 1/23/16, Newsweek
"El Chapo Shows The Folly of the War on Drugs," 1/21/16, Time
"Less Rape On Campus? Get Rid of College Football," 1/7/16, US News and World Report
"Report: Rape Rates at Big Football Colleges Spike on Game Day," 1/16, CBS News
"What We Can Learn From That Paper About Campus Rape on Game Days," 12/15, Slate
"The Disturbing Truth About College Football and Rape," 12/2015, The Washington Post
"College Football, Parties and Rape," 12/2015, Inside Higher Ed
"With Less Money, Colorado's Birth Control Program Feels the Pain," 8/2015, The Denver Post
"Does Child Abuse Rise During a Recession?" 5/2013, Freakonomics.com
"Ticket to Drink Opens Door to Health Woes," 3/2013, Illawara Mercury
"How Does Football Success Affect Student Performance?" 10/2012, The Chronicle of Higher Education
"Rethinking The Benefits of College Athletics," 3/2012, Forbes
"How Big-Time Sports Ate College Life," 1/2012, New York Times
"College Football Victories = Worse Grades?" 1/2011, Freakonomics.com
"Study Links Winning Football and Declining Grades," 1/2011, New York Times
"Football Team Wins, Grades Plummet," 12/2011, The Wall Street Journal
"Study: Male Students' Grades Drop When Football Teams Win," 12/2011, USA Today
"Winning Football, Declining Grades," 12/2011, Inside Higher Ed
"Study: As Ducks Win, Male Grades Drop," 12/2011, ESPN
"Guys' Grades Suffer When College Football Teams Win," 12/2011, The Atlantic
"Academic Probation Hits College Guys Harder," 5/2010, Science Daily

Updated January 13, 2023

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

Alliance for Hippocratic Medicine, *et al.*, Plaintiffs, v. U.S. Food and Drug Administration, *et al.*, Defendant.	Case No. 2:22-cv-00223-Z

DECLARATION OF LUU IRELAND, MD, MPH, FACOG

I, Luu Ireland, pursuant to 28 U.S.C. § 1746, declare under penalty of perjury that the following is true and correct to the best of my knowledge and belief, and that these statements are based on my personal knowledge as well as information made known to me in the course of my medical practice:

1. I am a board-certified Obstetrician-Gynecologist ("Ob-Gyn") physician and attending physician at the University of Massachusetts Memorial Health in Worcester, Massachusetts. At UMass Memorial Health, I serve as an Assistant Professor of Obstetrics and Gynecology and Departmental Director of Diversity, Equity and Inclusion. I also serve as a staff physician for Planned Parenthood League of Massachusetts. I am board-certified in both Obstetrics and Gynecology and Complex Family Planning. In my day-to-day practice, I provide full-spectrum obstetric and gynecologic care. In my gynecologic role, I provide routine annual exams, contraceptive counseling for pregnancy prevention, treatment for a range of gynecological issues including abnormal uterine bleeding, management of abnormal pap smears, treatment of uterine fibroids and vulvovaginal disorders, and routine gynecologic surgery. In my obstetric role, I

participate in both inpatient and outpatient management of pregnancies, including prenatal care, labor and delivery, and postpartum care. This includes diagnosis and treatment of pregnancy complications and pregnancy loss. I also provide family planning services through Planned Parenthood League of Massachusetts. Approximately 30% of my clinical time is spent providing abortion-related care.

2. I earned my masters degree from the Mailman School of Public Health at Columbia University in New York in 2005. I graduated with a medical doctorate from the David Geffen School of Medicine at the University of California, Los Angeles (UCLA) in 2009 and completed my residency in Obstetrics and Gynecology at Women and Infants Hospital of Rhode Island/Warren Alpert School of Medicine at Brown University in 2013. I completed fellowship training in Complex Family Planning at UCLA in 2015. I joined the faculty of UMass Memorial Health in 2015 where I continue to serve as a clinician, educator, and leader to the department of Obstetrics and Gynecology.

3. In my current position, I have been active in undergraduate and graduate medical education for medical students, residents, and undergraduates. For medical students, I provide both didactic education during the 2nd year Reproductive Health Curriculum and clinical education during the 3rd year clerkship rotation and 4th sub-internship rotations and electives. I also serve as a Longitudinal Preceptor to provide clinical experience and teaching to 4 assigned medical students per year during their 1st and 2nd years of medical school. I am also a Faculty Advisor for the Women's Health Elective, a student run curriculum covering the public health aspects of reproductive health care. Finally, for 5 years, I served as a Learning Communities mentor in which I provided mentorship, support, and guidance to 6 to 12 medical students per year. Within this role, I taught physical exam techniques, history taking, medical documentation, and oral presentations.

For resident trainees, I support this educational process in a number of ways. In the clinic, I precept residents in performing outpatient prenatal, postpartum, and gynecologic care. In the operating room, I teach and supervise residents in a variety of gynecologic surgeries. On Labor and Delivery, I teach and supervise residents in the management of labor, pregnancy and postpartum complications, vaginal deliveries, and cesarean sections. As a Complex Family Planning specialist, I educate residents on the clinical considerations around contraception, abortion, and management of pregnancy loss. I teach residents how to provide patient-centered counseling around pregnancy prevention, termination, and miscarriage. I teach them how to perform medical and surgical care for abortion and pregnancy loss. This education takes place in the office, the operating room, Labor and Delivery, and at Planned Parenthood. My commitment to education goes beyond clinical teaching. I have also served as a research mentor to resident physicians and this work has resulted in several presentations at academic conferences. I have received several awards for my teaching, including the UMass Golden Apple awards, UMass Medical School Outstanding Medical Educator Award, and the Council on Resident Education in Obstetrics and Gynecology National Faculty Award for Excellence in Residency Education.

I have published book chapters on pregnancy loss in the first trimester[i], as well as Combined Oral Contraception[ii]. I also published a review article on pain control for outpatient gynecologic procedures[iii]. As a researcher, I have peer-reviewed publications on long-acting reversible contraception[iv], efficacy of medical and surgical abortion in the first trimester[v], and guidelines on preventive health care for women.[vi]

Leadership is a significant part of my role as a physician. Within the department, I serve as the Director of Diversity, Equity, and Inclusion (DEI). I lead initiatives to improve pregnancy related outcomes among Black and Latinx pregnant patients. I organize educational sessions for faculty

and residents on DEI related topics. I also serve as a statewide and national leader in reproductive health care. I am the current Chair of the Massachusetts section of the American College of Obstetricians and Gynecologists (ACOG). I also serve on the Committee for Maternal and Perinatal Welfare for the Massachusetts Medical Society. I am an active board member for the Planned Parenthood Advocacy Fund. On the national level of ACOG, I serve on both the Committee for Clinical Practice Guidelines in Gynecology as well as the Abortion Access and Expert Working Group.

In sum, I have been a practicing Obstetrician and Gynecologist for 14 years and in this time, I have cared for thousands of women. I have used this experience to educate and mentor the next generation of physicians and lead my field in the practice of evidence-based medicine. The health and well-being of women is my first and foremost goal and career mission.

4. I am a certified prescriber of Mifepristone under the REMS Program, have used it in the course of my practice, and continue to rely on the medication to ensure the best outcomes for my patients. Mifepristone is well known as part of the evidence-based regimen for medication abortion in the first trimester. Complications are exceedingly rare—both nationally and in my patient population—but include incomplete abortion or retained products of conception, excessive bleeding, or infection, which can be quickly resolved, typically with a surgical aspiration procedure. These extremely low risks are much lower than the risk of complications in carrying a pregnancy to term.

5. Suction dilation and curettage (D&C) is a form of surgical abortion and is a safe procedure that occurs in the first trimester (13 weeks gestation or less) to evacuate the uterus and remove products of conception. The pregnant person is placed in the same position as she would be for a pelvic exam. A speculum is placed in the vagina so that the cervix, or the opening of the uterus, is

visualized. A numbing medicine is injected around the cervix. The opening of the cervix is dilated until it can accommodate a plastic tube. Gentle suction is then used to empty the uterus. The whole procedure takes less than 5 minutes. In the second trimester (14 to 24 weeks), the procedure is known as a dilation and evacuation (D&E). The difference in this procedure is that pre-procedural medications or dilators are often needed to open the cervix to ensure patient safety. Additional instruments beyond suction may be needed to remove the pregnancy. These procedures can be performed in the office setting or in the operating room under sedation or general anesthesia, determined by patient preference. Complications are also exceedingly rare but can include heavy bleeding or hemorrhage, infection, retained products of conception, retained blood clots in the uterus, or uterine perforation. In my experience, these occur less than 1% of the time in first trimester cases and 1-2% of the time in the second trimester (risk increases with gestational age). These risks are much lower than the risk of complications in carrying a pregnancy to term.

6. Medical management of first trimester abortion is completed with a combination of Mifepristone and Misoprostol. Mifepristone (200mg) is a progesterone receptor antagonist, meaning it blocks and deactivates the receptor for progesterone, which is essential to support the pregnancy in the first trimester. In my judgment, there is also evidence that Mifepristone weakens the attachment of the pregnancy to the wall of the uterus and softens the cervix. Misoprostol (800mcg) is administered next and this causes uterine contractions and expulsion of the products of conception. In my practice, Mifepristone is given orally, in the office. For medication abortion, for which Mifepristone has FDA-approval, Misoprostol is administered within 0 to 48 hours following Mifepristone.

7. I have found that patients often prefer a medication management for abortion for various reasons, including the sense that it feels like a more "natural" process and the preference to avoid

surgery or anesthesia. Some patients have uterine anomalies such as large fibroids which make uterine evacuation by suction D&C challenging. There are also particular patient populations for which medical management is more appropriate. This includes patients who are survivors of abuse, including rape and incest, for whom pelvic exams can recreate severe trauma. Adolescent patients, who have not yet had a pelvic exam, frequently prefer medical management as a less invasive option. Finally, patients in the intensive care unit or trauma patients who have difficulty with the positioning required for suction D&C can benefit from medical management.

8. Prior to prescribing mifepristone, legal and medical ethics require providers, such as myself, to ensure that appropriate informed consent is obtained and that shared decision-making is effectuated by the patient and her family members, if she chooses. In ensuring that patients are fully informed when choosing among options for an unplanned or undesired pregnancy, I review all options including continuing the pregnancy to its natural conclusion and choosing parenting or adoption, and pregnancy termination via medical or surgical abortion. Once a patient chooses abortion, I review the risks and benefits of each modality. I usually explain that both medication and surgical abortion are safe, effective, and have no bearing on future fertility or risk of pregnancy complications. I describe how some patients choose medication abortion based on a preference to avoid a procedure and desire for a more "natural process" at home. I review that this process is more prolonged and can take hours to days to complete. I explain that follow-up is essential to ensure that the abortion is complete. I provide the patient with the Mifepristone Medication Guide and Patient Agreement, answer any questions, and ensure that the patient signs the Patient Agreement.

The process for medication abortion is as follows. A 200mg Mifepristone tablet is given in the office. This medication prepares the body to pass the pregnancy but does not work alone.

Misoprostol comes in 4 small tablets (200 mcg each) that need to be self-administered within 0 to 48 hours. Bleeding will occur within a few hours of Misoprostol administration. The bleeding can be heavy, with clots, and the cramping can be strong. In my experience, the vast majority of pregnancies will pass within 6 hours, after which the bleeding and cramping will get lighter and more closely resemble a menstrual period. The regimen has expected side effects that typically accompany the emptying of the patient's uterus, and these include fever, chills, nausea, vomiting, and diarrhea; these anticipated side effects are not considered complications and should resolve within 24 hours. Signs of complications include side effects that persist beyond 24 hours, bleeding in which the patient is completely saturating 2 maxi-pads per hour for 2 hours in a row, or severe pain that is worsening and unimproved with over-the-counter pain medications. Follow-up is required to ensure the pregnancy has completely passed, as there is a 1-4% percent chance of ongoing pregnancy depending on gestational age at time of abortion. As noted above, these complications can occur but, in my experience, do so very rarely.

Some patients prefer a surgical procedure due to the more predictable timeline to complete the abortion and the reduced need for follow-up. Some of these patients desire anesthesia during their abortion or prefer to avoid the heavy bleeding and cramping that can come with medication abortion. Some patients have contraindications to medication abortion including severe anemia, bleeding disorders, or inability to complete follow-up. When patients choose surgical abortion, I describe the procedure as well as the risks. For a suction D&C surgical abortion in the first trimester, the risk of a major complication C is less than 1% and these risks include severe pain, hemorrhage, infection, retained products of conception, retained blood clots in the uterus, or uterine perforation.

9. The information I provide to my patients is based on my years of training and experience both teaching new doctors and treating patients. I understand that use of all medications and medical procedures carry risks, including rare adverse events, and convey that understanding to patients as part of my regular medical practice. However, the use of Mifepristone has been tested clinically and used widely, with exceedingly low risks of side effects or adverse events. In my clinical practice, the benefits of Mifepristone far outweigh any potential risks.

10. As an example of the use of Mifepristone for my patients, I'd like to share my experience in caring for a 14-year-old girl who came to me with a 7-week pregnancy as a result of rape. She had the support of her mother, who was working with law enforcement to bring charges against her perpetrator. She strongly desired an abortion and to return to her normal ninth grade life. A surgical procedure to end the pregnancy would have been devastating and traumatic given her young age, lack of consensual sexual experience, and this very recent history of sexual trauma. She was so relieved to learn that we could offer her an abortion using pills alone. She went on to have an uncomplicated abortion at home with the support of her mother.

11. Another patient I cared for recently was a mother of six children who came to me with a 9-week unplanned pregnancy. She had been using the birth control patch, but due to a delay in changing her patch, she became pregnant. Her husband was in and out of her life, and did not reliably provide financial, social, or parenting support. She had 5 children living with her in a 2-bedroom apartment and was struggling to make ends meet. She could not conceive of how she would care for another child and adoption was not a choice that felt right for her. Because she was the sole and full-time parent for her children, ages 2 through 22, she could not take the time away from home, and arrange childcare and transportation, in order to have a surgical abortion. A

medication abortion with Mifepristone and Misoprostol allowed her to end the pregnancy safely and effectively, while maintaining her ability to parent and care for her children.

12. Another patient I cared for spent 10 years with an abusive partner. She finally pulled herself out of the relationship and obtained a divorce. The day the divorce was finalized, she found out she was pregnant. She was 8-weeks along when I met her. Knowing how unhealthy this relationship had been, and how long it took her to break free, she was confident that continuing the pregnancy would forever link her to her abuser. She strongly desired to end the pregnancy within the privacy of her own home. After 10 years of being in a relationship in which she had no power to make her own decisions, this was one of the first opportunities she had in a decade to make a choice for her own body.

13. I cared for another patient who had spent the last year recovering from severe postpartum depression and anxiety. This experience had rendered her unable to return to work and barely able to take care of her family. She had finally found a regimen of medications and therapy that was working to treat her crippling anxiety and panic attacks. She had finally decided on a return-to-work date. She finally had hope again. At the same time, she found out she was unexpectedly pregnant again. Upon learning she was 5-weeks pregnant, she sat in my office in tears thinking about reliving the same postpartum nightmare. She was also panicked about the idea of surgery and anesthesia. Knowing how severe and resistant her anxiety was, and observing her panic at the thought of surgery, I was grateful to offer her the option of medication abortion. She was relieved when she learned she had an option to end the pregnancy at home with the support of her husband nearby. She underwent an uncomplicated medication abortion at home. She became a long-term patient of mine, and each year, I get the honor of seeing her thrive as a mother, wife, and working individual.

14. I understand that Plaintiffs in this suit have asked the Court to revoke FDA's approval of Mifepristone. In my opinion, granting that request would cause substantial harm to patients and the medical practice because Mifepristone is safe. There are very few contraindications to the medication. Moreover, the drug has an excellent safety profile, with only exceedingly rare adverse events, and a very mild side effect profile.

Without Mifepristone, more patients will be forced to rely on surgical management for their abortions or forced to carry an unwanted pregnancy to term. Should the request to remove FDA approval of Mifepristone be granted, we would be eliminating a safe and effective treatment option for early abortion. To deny an evidence-based, safe and effective treatment goes against every part of my medical training and our profession's commitment to providing patient-centered care. Eliminating access to Mifepristone would unequivocally and unquestionably cause harm to patients without *any* clinical benefit. It would force patients into situations in which their autonomy for care is limited. I would no longer be able to explain that surgical and medical management of abortion are substantially equal in efficacy and risk. And this would coerce patients into having surgery that many are desperate to avoid, or facing the risks attendant to continuing pregnancy and childbirth against their own wishes.

There is also a large, negative public health impact should FDA approval of Mifepristone be revoked. Health care has never been in bigger crisis. Three years into the pandemic, COVID remains a leading reason for hospitalization. Health care workers have left the workforce in droves and medical facilities and hospitals are facing unprecedented issues in short staffing. Clinician burnout is a major issue and physician and nursing shortages are only expected to worsen. With this in mind, any increase in demand for limited resources available in the clinic or Operating Room is highly problematic. And this increase is guaranteed should Mifepristone be made

unavailable. More patients choosing surgical abortion will invariably lead to increased demand on resources for procedures in both the office and the operating room.

Dated January 13, 2023

Luu Ireland, MD, MPH, FACOG

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UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

Alliance for Hippocratic Medicine, *et al.*, Plaintiffs, v. U.S. Food and Drug Administration, *et al.*, Defendant.	Case No. 2:22-cv-00223-Z

DECLARATION OF EVELYN KIELTYKA

I, Evelyn Kieltyka, pursuant to 28 U.S.C. § 1746, declare under penalty of perjury that the following is true and correct to the best of my knowledge:

1. I am the Senior Vice President of Program Services for Maine Family Planning and Primary Care Services, where I have worked for nearly 25 years. In this position, which I have held since 1995, I oversee program development and quality assurance relating to all aspects of reproductive healthcare. I submit this declaration in support of Defendants' Opposition to Plaintiffs' Motion for a Preliminary Injunction in the above-captioned matter. Unless otherwise stated, the facts set forth herein are true to my own personal knowledge.

2. I am educated and trained as a family nurse practitioner ("FNP"). I was certified as an FNP by the American Nurses Credentialing Center in 1995 and recertified most recently in 2020. I currently hold an active registered nurse and an Advanced Practice Registered Nurse Practitioner license in Maine. I received a Master's of Science in Maternal-Child Health at the Harvard T.H. Chan School of Public Health and a Master's

in Nursing at Simmons College in 1992; and I earned my certificate as a Family Planning Nurse Practitioner at the College of Medicine and Dentistry of New Jersey in 1979. I received my Bachelor's of Science in Nursing degree at Sacred Heart University in 1987.

3. I have provided clinical care as a registered nurse and Advanced Practice Registered Nurse ("APRN") throughout my career. In 2000, I was awarded the Nurse Practitioner of Excellence Award by the American Academy of Nurse Practitioners and the Maine Nurse Practitioner Association ("MNPA"). I have also been the President of the Board of Directors of the MNPA, a position I held from 2015 to 2017 and 1995 to 1997.

I. MAINE FAMILY PLANNING'S PROVISION OF HEALTHCARE SERVICES

4. Maine Family Planning ("MFP") is a non-profit corporation incorporated in Maine and headquartered in Augusta, Maine. For over fifty years, Maine Family Planning has worked to ensure that people across Maine have access to high-quality, affordable reproductive healthcare. To carry out its mission, MFP directly operates eighteen health centers throughout Maine.

5. MFP's clinics are located in Augusta, Bangor, Belfast, Calais, Damariscotta, Dexter, Ellsworth, Farmington, Fort Kent, Houlton, Lewiston, Machias, Norway, Presque Isle, Thomaston, Rumford, Skowhegan and Waterville. MFP provides services in twelve counties that are more than 50% rural and eight counties that are more than 80% rural.

6. At our health centers, MFP provides a range of healthcare services, including but not limited to: annual gynecological exams; screening for cervical and breast cancer; family planning counseling; contraceptive services; preconception consultation; screening, diagnosis, and treatment of urinary, vaginal, and sexually transmitted infections;

endometrial and vulvar biopsy; hormone therapy and other services for transgender clients; services for mid-life women; and miscarriage care, as well as abortions. In addition, MFP has an extensive, well-established referral network that connects clients to comprehensive primary care and other diagnostic screenings and services, if not offered on site.

7. MFP has been providing surgical abortion care since 1997, and has been offering medication abortion services since shortly after the U.S. Food and Drug Administration approved mifepristone for use in the United States in 2000.

8. While MFP offers medication abortion to patients at each of its 18 sites, surgical or aspiration abortion is only available at its one clinic in Augusta.

9. With a medication abortion, the patient takes a series of medications to terminate the pregnancy and empty the uterus. A patient will first take mifepristone, which blocks the body's production of progesterone. Progesterone is a hormone necessary for the pregnancy to continue, and taking mifepristone terminates the pregnancy. Second, 24-48 hours after taking mifepristone, a patient will take misoprostol. This medication causes cramping and bleeding and will cause the uterus to expel its contents, similar to a miscarriage.

10. With a surgical or aspiration abortion, at least at MFP, a trained and licensed clinician sedates the patient with local anesthesia before performing the procedure. After the procedure, the patient recovers at the health center under supervision. As noted above, MFP only offers surgical abortion at its Augusta clinic, and it is available there up to 14.0 weeks as dated from the first day of the patient's last menstrual period ("LMP").

11. The number of abortions MFP provides varies from year to year, but the percentage of those abortions that are provided through medication has continued to rise.

12. In 2021, MFP provided 683 abortions in total, 423 (61%) of which were medication abortions. 378 of the medication abortions that MFP provided in 2021 were provided at MFP's non-Augusta clinics, where medication abortion is the only option available.

13. In 2022, MFP provided 842 abortions in total, 595 (70%) of which were medication abortions. 486 of the medication abortions that MFP provided in 2022 were provided at MFP's non-Augusta clinics, where medication abortion is the only option available.

14. Patients may obtain a medication abortion at MFP through telehealth appointments or in-person at each of MFP's 18 health centers.

15. Patients may obtain a surgical or aspiration abortion only in person at MFP's Augusta clinic.

16. MFP ensures that its providers who perform abortions are appropriately trained and licensed. For instance, our providers who perform surgical abortion have performed more than the 25 to 50 surgical abortions with supervision. The surgical abortions that they perform at MFP's Augusta clinic maintain their hand skills, and MFP ensures that these providers work with sterilized and appropriately maintained equipment.

17. Besides MFP, the only other places in Maine where medication and surgical abortion services are publicly available (*i.e.*, generally open to new patients) are: (1) Planned Parenthood of Northern New England in Portland; and (2) the Mabel Wadsworth Center in Bangor. Both provide abortion care only one day a week (with very few exceptions). Although there are two hospitals in Maine that occasionally provide abortion services—Maine Medical Center in Portland and Central Maine Medical Center in

Lewiston—both generally only treat established patients, among other limitations on their services.

II. REASONS MEDICATION ABORTION IS THE PREFERRED OPTION FOR SOME PATIENTS

18. Based on my experience, I know that there are a variety of reasons that medication abortion is the necessary and/or preferred option for many patients. Some of those reasons are medical, and others are based on the patient's non-medical circumstances (*e.g.*, timing, location, or need for privacy). As explained below, medication abortion is instrumental in removing barriers that would otherwise make it more difficult, and in some cases impossible, for MFP's patients to receive the health care they need.

19. First, there are medical reasons why medication abortion is medically indicated for certain patients, rather than surgical abortion. This is because some patients come to MFP with pre-existing conditions that would make surgical abortion a riskier option for them over medication abortion.

20. For example, MFP has treated patients who are allergic to anesthesia, and specifically who are allergic to lidocaine, which is the local anesthetic MFP uses when it provides surgical abortions. Allergic reactions to lidocaine can include anaphylaxis, urticaria, edema, bronchospasm, unconsciousness, hyperventilation, nausea, vomiting, and changes in heart rate or blood pressure. Because anesthesia is provided for surgical abortion, an allergy to anesthesia makes surgical abortion a riskier and more complicated method for patients with that condition. Because medication abortion does not require the use of anesthesia, it is the preferred method for terminating such a person's pregnancy.

21. To provide another example, based on my experience, medication is the most appropriate abortion method for patients with a bicornuate uterus. A bicornuate uterus

is a uterus that is shaped irregularly; instead of being pear-shaped, it has a heart-shaped appearance with a septum going down its center and appears to have two sides rather than one hollow cavity. When a patient has a bicornuate uterus, aspiration is less likely to terminate a pregnancy successfully because it is difficult to fully evacuate the uterus using suction. Accordingly, medication abortion is the best and least risky option for those patients.

22. Similarly, based on my experience, medication abortion is often the better option for patients with cervical stenosis. Cervical stenosis is a narrowing of the passageway through the cervix. This narrowing can act as a barrier to the uterine cavity, which may make surgical abortion nearly impossible or else cause severe tearing. By contrast, medication abortion allows evacuation of the uterus without that physical trauma and additional risk for patients with cervical stenosis.

23. I also know that there are non-medical reasons why patients choose medication abortion, including because it offers a greater degree of privacy and/or control over the timing of their abortion than surgical abortion. Even though aspiration abortion itself takes only 5 to 10 minutes, a patient typically spends between 3 and 5 hours at the clinic, including time spent receiving counseling, giving informed consent, waiting on rooms and instruments to be prepared, and recovering under observation (usually 30 to 45 minutes). MFP also requires patients to have a designated driver to take them home once they are discharged.

24. By contrast, an in-person medication abortion appointment requires only about 25 to 40 minutes, which consists of confirming gestational age and then providing detailed counseling about the procedure and after-care instructions, answering any patient

questions, and going over the patient agreement and informed consent forms. After that, the patient receives their prescription and can take their first pill at the clinic or wait until they get home. Either way, because the patient can complete their abortion at home, there is no need to involve a third party as a designated driver.

25. Alternatively, MFP can provide the same option through a telehealth visit, which a patient can conduct from a remote location of their choosing. The medication can then be safely taken in the comfort and privacy of their own home, without the assistance of another person in visiting and leaving a health care center.

26. Based on a patient's personal circumstances, there are myriad reasons why a patient may find the privacy of medication abortion to be a better fit for their needs, either in person or through a telehealth appointment.

27. For example, medication abortion through telehealth is often a preferred option for patients who have busy work schedules, or those who have kids and would otherwise need (or be unable to obtain) childcare. Some of our patients choose telehealth because they do not have access to a car or public transportation. And some patients choose telehealth because it provides a better opportunity for confidentiality, since the patient does not have to explain their absence from work or home during certain hours.

28. On the other hand, some patients prefer to receive a medication abortion through an in-person visit, and that is an option that we always make available to them. Some patients live in small homes with other people and cannot find a private place to engage in a telehealth appointment. Some of our patients do not have access to broadband or any other Internet service. And some patients find comfort in meeting with a clinician in person.

29. Even when a patient opts for an in-person visit to obtain a medication abortion, the patient still is able to take the first pill (mifepristone) and the second pill (misoprostol) later, in order to expel the contents of their uterus at a time and place that works best for them.

30. Medication abortion is also often a better option for persons who need a less physically invasive procedure, which is often especially important for our patients who are victims of rape or abuse.

31. Finally, the wider accessibility of medication abortion also ensures that it is more equally available to pregnant persons of lesser means. In Maine, and in many places across the country, surgical abortion is available only at certain physical locations and at certain times. For some pregnant persons, particularly those with lower incomes, this limited availability is prohibitive. But because medication abortion can be prescribed following a telehealth visit or at a local clinic, and the drugs can be mailed to and taken at a person's home, medication abortion ensures that these services are available on a more equitable basis.

32. A few recent examples from MFP's practice may help to illustrate some typical circumstances in which medication abortion benefits our patients.

33. In one example, a twenty-nine-year-old patient without family support had nobody to help her with transportation to and from a surgical abortion. The patient was able to obtain a medication abortion instead at her local MFP center, where she received the care she needed without having to involve a third party.

34. Another recent twenty-two-year-old patient chose medication abortion via telehealth because surgical abortion would have taken her away from school and interfered

with her ability to take her exams. That patient was a college student with finals approaching, and a forty-minute visit to the local MFP center site fit her needs far better than the four-hour drive, coupled with a 4-5 hour visit at a health center offering surgical abortion.

III. IMPACT OF ELIMINATING ACCESS TO MIFEPRISTONE ON AVAILABILITY OF ABORTION CLINICS IN MAINE

35. If mifepristone, and by extension medication abortion, is no longer an option, it would dramatically affect MFP and the availability of abortion more generally in Maine and across the country.

36. To start, MFP would have no choice but to eliminate abortion services altogether at 17 of its 18 locations, leaving only its abortion practice in Augusta.

37. It would not be feasible for MFP to begin providing surgical abortions in the 17 satellite locations for several reasons. First, the clinicians who work at those clinics are not trained to provide surgical abortion, and it is infeasible for MFP to train providers at those clinics to do so. As noted above, the training necessary to perform aspiration abortions is intense—involving more than 25 supervised abortions—and requires upkeep. Some of our satellite clinics do not have that many abortions in any given year, and thus cannot provide the requisite opportunities for that training. We would have to bring clinicians from long distances to supervise and provide that training and/or the local clinicians from our satellite clinics would have to travel elsewhere to receive their training. That travel and associated training would be time-consuming and costly for our clinicians, and it would take those clinicians away from providing health care services (including, but not limited to, abortion services) in their regular locations. Given the demands on our clinicians' time and the critical services they provide to their communities, it would be

infeasible for them to acquire the training necessary to provide aspiration abortion at our non-Augusta clinics.

38. In addition, because some of MFP's remote sites provide only a handful of abortions each year, clinicians at those remote sites would have difficulty keeping their skills and training in aspiration abortion up-to-date over time—even if we were able to train clinicians to perform aspiration abortion at our satellite locations at the outset. Indeed, some of our most rural locations only provide 1 or 2 abortions per year (although the ability to obtain an abortion is critical for those 1 or 2 patients in rural locations who would otherwise have no other options in their geographic vicinity). This would mean, clinicians from our satellite clinics would have to travel regularly to Augusta in order to practice their skills—again, taking them away from their local practice where they are often the only healthcare provider available to patients in their rural locations.

39. Even if MFP were able to train clinicians to provide surgical abortions at our non-Augusta health centers or hire clinicians with sufficient training, it would still be infeasible (and in some cases physically impossible) for those local clinics to obtain the necessary space and equipment to provide surgical abortion. Those clinics do not currently have the requisite machinery, which costs approximately $2,000-$3,000, nor are they equipped with the other necessary instruments for dilation and anesthesia. At least three of our clinics (in some of our most rural locations, *e.g.*, Rumford and Skowhegan) are so small that the requisite equipment and materials would not even fit in the clinics' physical space.

40. If medication abortion became unavailable, Maine would be left with just three remaining publicly-accessible health centers where a woman can obtain abortion care in Maine: (1) MFP's Augusta clinic; (2) PPNE's Portland Health Center; and (3) Mabel

Wadsworth Center, located in Bangor, Maine. This would mean that more than half of Maine women would live in the 13 remaining counties without an abortion provider, and the distances many women would have to travel to obtain an abortion would increase substantially.

41. Under those circumstances, many patients would have to travel over 100 miles to obtain abortion care in Maine. Moreover, due to Maine's challenging weather conditions, certain roads typically are completely impassable during parts of the winter, particularly in rural Aroostook and Washington Counties. Even if patients would be able, in theory to travel to Augusta, given the lengthy distances, they may need to drive up the night before. And, because it might not be safe for them to then drive many hours home, potentially alone, after a medical procedure, it might be necessary to stay overnight again. Thus, traveling from these remote locations would be at least a two-day, and potentially a three-day, affair for many patients seeking abortion services.

42. If MFP were unable to provide medication abortion at its 17 non-Augusta clinics, many of which are located in extremely rural areas, I believe it would be a tremendous hardship for patients seeking abortion in large swaths of the state.

43. MFP's abortion patients routinely report that they do not have, and will not be able to find, the money they need to travel to a clinic in a different city for abortion care.

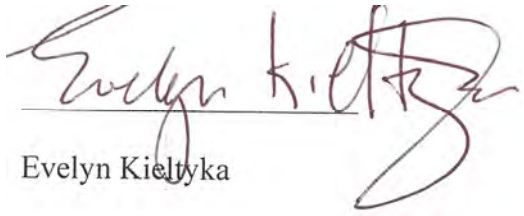
44. Approximately 70% of MFP's patients received Medicaid coverage or otherwise needed financial support for their abortion in 2022. Our patients often work in low-wage jobs that do not offer paid time off or sick leave, and often have unpredictable schedules that may only be set a few weeks, or even just a few days in advance. Many also

have childcare responsibilities that significantly complicate and limit their scheduling options.

45. For patients who are nonetheless able to overcome the burdens associated with increased travel distances, my experience with patients has shown me that travel will still inevitably delay access to abortion. Delayed abortion care is associated with greater health risks. The risks of complications increase with increasing gestational age. Moreover, every day a woman remains pregnant, she faces the continued risks of complications of pregnancy.I declare under penalty of perjury that the foregoing is true and correct.

I declare under penalty of perjury that the foregoing is true and correct.

Executed January 13, 2023



Evelyn Kieltyka

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

Alliance for Hippocratic Medicine, *et al.*, Plaintiffs, v. U.S. Food and Drug Administration, *et al.*, Defendant.	Case No. 2:22-cv-00223-Z

DECLARATION OF KATHERINE B. GLASER, MD

I, Katherine Glaser, pursuant to 28 U.S.C. § 1746, declare under penalty of perjury that the following is true and correct to the best of my knowledge and belief, and that these statements are based on my personal knowledge as well as information made known to me in the course of my medical practice:

1. I am a board-certified Obstetrician-Gynecologist ("Ob-Gyn") physician and attending physician at a regional hospital serving an indigenous population in Northern Arizona. I also serve as a Clinical Assistant Professor of Obstetrics and Gynecology at the University of Arizona, Tucson and the University of Arizona, Phoenix. I also work as an independent contractor with a clinic to provide abortion care in Northern Arizona. I am board-certified in Obstetrics and Gynecology with a sub-specialty in Complex Family Planning. In my day-to-day practice, I participate in both inpatient and outpatient management of pregnancies, which includes treating patients undergoing pregnancy loss and other complications that arise during pregnancy and delivering babies. My practice is in a rural, underserved area with high rates of poverty and

unemployment, and in the work regarding abortion, due to limited availability of abortion services in the state of Arizona, those seeking an abortion often travel many miles for these services.

2. I graduated from the University of Arizona College of Medicine in Tucson, Arizona in 2008, and completed my residency in Tucson in 2012. Additionally, I completed a fellowship in clinical research at the University of California, Davis in 2022. I have worked as an Ob-Gyn for 14 years and provided abortion services through most of those years of practice.

3. In my current position, I actively teach obstetrics to residents and medical students. I am also an active member of the American College of Obstetricians and Gynecologists ("ACOG") and have held ACOG offices in the state of Arizona, and I am currently the ACOG co-Legislative Chair for the state of Arizona. I am a Rural Director on the Board of Directors for the American Medical Association. As a fellow, I authored publications about family planning and diabetes in pregnancy. In these roles, I have 14 years of clinical experience, have an active, broad clinical practice, and am engaged in advocacy at the state and national level.

4. I am familiar with the medication mifepristone, have used it in the course of my practice, and continue to do so. I am also a certified prescriber of Mifeprex under the Mifeprex REMS Program. Because I primarily practice in a federally funded facility, abortion is only provided in relatively rare circumstances that fall within the exceptions allowed by the Hyde Amendment, *i.e.*, circumstances where the pregnancy results from rape or incest, or the patient experiences complications that could seriously threaten her life or health should the pregnancy continue. Notwithstanding the relative infrequency of abortion care in my primary practice, through my work as an independent contractor at a clinic providing abortion care, I have used and continue to use the combination of mifepristone and misoprostol for medication abortion for numerous patients.

5. For patients who choose to end a pregnancy, counseling about the options to end the pregnancy is provided. Patients are informed about a surgical abortion, which would use dilation and suction to remove the pregnancy tissue from the uterus. The option of medication abortion is also explained, and patients are informed that this would include the use of mifepristone followed by the use of misoprostol in 24-48 hours. The risks of both options are explained in full, as is the expected course of treatment.

6. In accordance with the Risk Evaluation and Mitigation Strategy (REMS) related to mifepristone, as well as Arizona state law, if a patient elects to have a medication abortion, at the first visit, the gestational age of the pregnancy is determined and options are explained. If the pregnancy is 70 days gestational age or less, medication abortion is an option. Under Arizona state law, the patient must then wait at least 24 hours before returning to the clinic for another appointment. At this appointment, the patient signs a consent form and a Patient Agreement to confirm that she has been informed about risks of mifepristone and has received the Medication Guide and Patient Agreement. She undergoes a pelvic exam, as required by state law, and then is given the mifepristone to be taken under direct observation in the clinic, as required by state law. Misoprostol is dispensed, as well as medication for nausea and a prescription for medication to help with cramping, if needed. The patient is instructed to take the misoprostol 24-48 hours after the mifepristone, and extensive counseling is given about when to call for assistance. The patient is also given a follow-up appointment. Adverse events are very rare with the mifepristone and misoprostol regimen, and the efficacy rate of the regimen is 98%.

7. Though medication abortion takes more time, many patients elect this method due to the desire to avoid what they may see as an invasive procedure if they select a surgical abortion. They may view the medication abortion as a more natural process. There may be other factors such as

not having a ride home from a clinic, especially if it is far from home, if they receive sedation during a procedural abortion. All factors being considered, what is important is to support patient autonomy in selecting between the methods, both of which are safe and effective, the one that best suits the patient's needs. This is a basic principle of medical ethics.

8. Prior to prescribing mifepristone, legal and medical ethics require clinicians, such as myself, to ensure that appropriate informed consent is obtained and that shared decision-making is effectuated by the patient and, if she chooses, her family members or other trusted persons. In ensuring that patients are fully informed when choosing among options, I describe all available options and the expected outcome as well as any associated risks. The patient is also, of course, screened for any of the conditions which would make medication abortion unsafe, such as inability to access emergency assistance in the rare instance it might be needed or medical conditions such as bleeding disorders, marked anemia, or porphyria, as examples. The patient and I also discuss circumstances that could make one option more appealing than another, such as lack of transportation or support at home. We discuss pros and cons of a medication or a surgical procedure. While medication means the patient can expect bleeding and cramping at home, choosing medication would allow the patient to avoid a procedure, if this is desired. Patients are also informed that the medication has a small risk of failure, so follow-up is important. Research shows that patients are most satisfied with care when they have the autonomy to choose the treatment that best suits them.

9. The information I provide to my patients is based on my years of training and experience both teaching new doctors and treating patients. I understand that all medications and medical procedures carry risks, including rare adverse events, and convey that understanding to patients as part of my regular medical practice. But the benefit of the mifepristone and misoprostol regimen

for medication abortion is that it provides a highly effective method of treatment. While complications are rare, they might involve heavier than expected bleeding or an incomplete expulsion of the pregnancy, which can be treated with additional medication or with a surgical procedure, depending on the circumstances or patient preference.

10. In my experience, I have often found that patients select medication abortion for a variety of reasons, including: privacy, control of time, and to avoid an invasive procedure. Based on my years of practice and teaching, my understanding of the published medical literature, and the requirement, described above, to ensure informed consent when counseling patients considering medication abortion, I counsel my patients about the risks of mifepristone to include significantly heavier than expected bleeding or incomplete procedure, and the very rare complication of infection. For a surgical procedure, the risks include bleeding, infection, and damage to the uterus, but the risk of an incomplete procedure is very small. As a physician, I understand that the FDA undertakes a careful assessment regarding the risks and benefits of any medication it approves, and in mifepristone's long history of use in this country and others, clinicians know that the medication is safe and efficacious and that its risks or contraindications are well known.

11. In particular, I have found that patients who are victims of abuse, including rape and incest, may find medication abortion to be a less invasive choice that avoids retraumatizing them. All patients, whether they have been abused or not, value autonomy over their bodies and making informed decisions about their health care, especially in the situation in which they may choose to end a pregnancy.

12. Those who seek abortion do so for many reasons and are of all ages and relationship statuses. I have cared for women who are young and working to achieve their educational and career goals, but experienced a failure of their chosen contraceptive method through no fault of

their own. Some already have families for which they are caring, and they know they do not have the means to support another family member. Others are victims of rape or incest, and they do not wish to continue a pregnancy resulting from that abuse. For all of these women, it is important to respect their rights and autonomy by allowing them to proceed with an abortion using the best method for them when considering their health and circumstances.

13. I understand that Plaintiffs in this suit have asked the Court to revoke FDA's approval of mifepristone. Based on my review of Plaintiffs' submissions, they appear to argue that revoking mifepristone's approval is necessary to address what they claim are risks from the use of mifepristone, but the claimed risks are unsupported by the robust literature examining the safety and efficacy of mifepristone. Eliminating mifepristone would, in my judgment, serve to worsen health outcomes, and for all the mentioned reasons, it is important to continue to allow the provision of mifepristone so that patients may obtain the care that best advances their health and well-being. Recent literature shows that restricting access to abortion worsens health outcomes and increases suicidality, as shown in an analysis of maternal death and morbidity in states that restrict access to abortion. Revoking FDA approval of a safe, effective medication would not help women as the Plaintiffs state, but would rather produce harm for women.

Dated: January 13, 2023

Katherine Glaser, MD

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

Alliance for Hippocratic Medicine, *et al.*, Plaintiffs, v. U.S. Food and Drug Administration, *et al.*, Defendant.	Case No. 2:22-cv-00223-Z

DECLARATION OF KATHERINE McHUGH, MD

I, Katherine McHugh, pursuant to 28 U.S.C. § 1746, declare under penalty of perjury that the following is true and correct to the best of my knowledge and belief, and that these statements are based on my personal knowledge as well as information made known to me in the course of my medical practice:

1. I am a board-certified Obstetrician-Gynecologist ("Ob-Gyn") physician at Women's Med Health Center Indianapolis and Partners in Abortion Care in College Park, Maryland. I also serve as an Associate Professor of Clinical Ob-Gyn at the University of Cincinnati, and owner of Indiana Pelvic Pain Specialists. In my day-to-day practice, I participate in both inpatient and outpatient management of pregnancies, which includes treating patients experiencing complications that arise during pregnancy and patients who wish to terminate their pregnancy. I provide abortion care in Indiana, Ohio, and Maryland, as permitted under the relevant state laws. I graduated from Indiana University School of Medicine in Indianapolis in 2011 and completed my residency in 2015. I joined the faculty of Indiana School of Medicine Department of Ob-Gyn upon graduation.

2. In my current position at the University of Cincinnati, I teach obstetrics and gynecology to residents, fellows, and medical students, and collaborate with nurses, midwives, and practitioners of many other disciplines. While at Indiana University, I served as one of the Associate Residency Program Directors and developed state-wide training programs for improving health outcomes of both mothers and babies. I have held multiple national Board positions, including on the Executive Board of the American College of Obstetricians and Gynecologists (ACOG) and Physicians for Reproductive Health. In addition to continuing to practice in an academic setting and teaching learners, I also started a small private practice treating patients with chronic pelvic pain, a topic on which I have published national guidance through ACOG. In these roles, I have delivered thousands of healthy babies to healthy parents over my twelve years of professional practice, as well as supported hundreds of families through the challenging decisions around pregnancy complications, terminations, and infertility.

3. I am familiar with the medication Mifepristone, have used it in the course of my practice, and continue to do so. I am also a certified prescriber of Mifeprex under the Mifeprex REMS Program.

4. For patients seeking to terminate an early pregnancy, I offer a choice between a medication regimen or a surgical procedure. Until 10 weeks gestation, pregnancy termination by medication abortion is an option. This regimen consists of Mifepristone 200mg orally followed by Misoprostol after 24-48 hours. These medications induce bleeding and shedding of the early pregnancy without need for instruments or procedures. Surgical abortion is performed anytime the patient declines medication abortion or if the patient is unstable and needs urgent intervention, or if the patient is unable to reliably attend follow-up appointments or seek urgent medical attention. While the

specifics of the procedure vary based on gestational age, the patient has a quick and simple procedure to stretch the cervix and remove the pregnancy tissue from the uterus.

5. Mifepristone is a small pill that, in the clinics where I practice, is dispensed at the clinic as required by state law. In both Indiana and Ohio, Mifepristone must be administered by an in-person physician, who watches the patient swallow the pill in the office. (Of note, this observation process has no medical indication but is required due to state regulation.) In the clinics where I practice in these states, Misoprostol is likewise dispensed at the clinic providing abortion care, and the patient takes it at home 24-48 hours after the Mifepristone. By contrast, in Maryland there are no laws mandating in-person observation of a patient taking Mifepristone or that it be dispensed by a physician. Patients in my Maryland practice are evaluated and counseled by me or one of my physician partners, after which the patient takes Mifepristone with a Registered Nurse prior to discharge home. Telehealth is also an option for patients in Maryland, whereas medication abortion provided via telehealth was specifically banned by Indiana and Ohio. After taking Misoprostol, the patient is expected to experience bleeding and cramping starting within a few hours, during which the pregnancy tissue passes. Medication abortion is 96-98% effective with very low rates of complication. ACOG Practice Bulletin, https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2020/10/medication-abortion-up-to-70-days-of-gestation.

6. I have found that patients often prefer a medication abortion for various reasons, including being able to plan their recovery time around family schedules, work, and other responsibilities, maintaining privacy, the perception that it is a more natural end to the pregnancy, as well as avoiding the more invasive surgical procedure. Based on my years of practice, my understanding of the published medical literature, and the requirement, described above, to ensure informed consent when counseling patients, I counsel my patients that medication abortion is safe and very

effective, making it an excellent choice for early pregnancy termination, and that, although medication abortion takes longer than a surgical abortion, the patient has more control over the process. The patient must be able to assess their symptoms and obtain transportation to a medical facility, should that become necessary, in order to proceed with medication abortion. If patients are unable to assess their symptoms or get medical help in the case of an emergency, the patient is not a candidate for medication abortion and must choose between surgical abortion and continuing the pregnancy. I also counsel the patients on the high safety and efficacy of medication abortion, as well as the preservation of future fertility and a discussion of any contraceptive needs. In particular, I have found that patients who are victims of abuse, including rape and incest, may find medication abortion to be a less invasive choice that avoids retraumatizing them and returns control over their bodies rightfully back to the victim.

7. Prior to prescribing Mifepristone, legal and medical ethics require providers, such as myself, to ensure that appropriate informed consent is obtained and that shared decision-making is effectuated by the patient and any family or friends the patient chooses. In ensuring that patients are fully informed when choosing among options, I always speak with the patient alone to screen for coercion or doubt in the decision. I provide the patient with the Mifepristone Medication Guide and Patient Agreement, answer any questions, and ensure the patient signs the Patient Agreement. We discuss the patient's options, based on medical history and gestational age, as well as the risks and benefits of each option, and answer all questions the patient has around the process. Included in all discussions of risk are the specific risks with each medication. Mifepristone is well studied in pregnancy termination and, as noted, has the expected effects of contributing to uterine cramping and bleeding. Mifepristone is not used in patients with known allergy to Mifepristone, an intrauterine contraceptive device in place, or an ectopic pregnancy (a pregnancy implanted outside

of the uterus). Mifepristone is also avoided in patients with bleeding disorders, with steroid-dependent medical conditions, and in patients taking blood thinning medications. Medication abortion with Mifepristone is much safer in patients with significant medical problems or complicated surgical histories which would make either surgical abortion or anesthesia more risky than normal. Patients who are very young also benefit from medication abortion because it avoids the need for a pelvic exam.

8. The information I provide to my patients is based on my years of training and experience both teaching new doctors and treating patients. I understand that all medications and medical procedures carry risks, including rare adverse events, and convey that understanding to patients as part of my regular medical practice. Mifepristone allows for the safe expulsion of pregnancy tissue without the additional risks of surgery or instruments, and allows patients the flexibility of timing the bleeding and cramping as they desire. Additionally, there is a high likelihood of success, up to 99.7% depending on gestational age, with increasing success correlating to decreasing gestational age. Complications of medication abortion are extremely low. Side effects found when Mifepristone is combined with Misoprostol include, in addition to bleeding and cramping, fevers or chills (32-69%), nausea (43-66%), dizziness (28-39%), vomiting (23-40%), diarrhea (23-35%), and headache (13-40%). These side effects are expected, however, as is the case with most or all medications, and are not considered to be complications. Need for transfusion (<0.1%) and need for surgical evacuation (<1%) are the most commonly reported adverse events. The notable adverse outcome that is possible with Mifepristone is possible teratogenic effects (causing birth defects or developmental malformations) on the fetus if the patient elects to continue the pregnancy after taking Mifepristone. All of these possibilities are extensively discussed with the patient, both verbally and in writing, prior to Mifepristone administration. Given the low incidence of adverse

events from Mifepristone, combined with its high efficacy, medication abortion is among the safest outcomes for a person desiring pregnancy termination. Of note, the mortality rate of legal, induced abortion is estimated to be 0.6 per 100,000 procedures, while the general mortality rate of continuing pregnancy is 8.8 per 100,000 live births, making legal abortion approximately 14 times safer than continuing pregnancy to delivery.

9. Healthcare providers, such as myself, rely on FDA to make a careful assessment of the risks and benefits of a medication and determine safety and efficacy; FDA's expert judgment informs our practice in treating individual patients. With the guidance of the FDA, clinicians make critical decisions about medications based on safety and efficacy. Interfering with FDA's process for assessing the risks and benefits associated with distribution of particular medications places patients and clinicians at risk.

10. As an example of the use of Mifepristone for my patients, I provide approximately 10 medication abortions per week in Indiana. While every patient's situation and reasoning is unique, there are certainly themes. I recently saw a patient at 7 weeks gestation who confided that her partner was physically, emotionally, and sexually abusive, and she needed her abortion to include bleeding so her partner would know she was not pregnant. When I called her a few weeks later, she spoke to me from the women's shelter, having successfully moved out and escaped her abuser.

11. Medication abortion also minimizes contact with the medical system. A woman told me that she didn't trust the medical system since her sister had died during childbirth, something the patient didn't believe could still happen in the United States. She chose medication abortion because it allowed her to be in control of what went into her body and minimized the number of people wanting to touch, examine, or perform a procedure on her body.

12. Another recent patient was at 9 weeks gestation and visited me the day before she was leaving for college. Though not a minor, she was accompanied by her mother, who supported the patient in her desire to prioritize her education before starting a family.

13. As a result of state-based abortion bans, patients are forced to travel to obtain abortion care, sometimes many states away, like the patient I saw recently from Louisiana. She talked about how she planned to leave immediately after taking the Mifepristone to start her 13-hour drive home so that she could rest in her own bed when the bleeding and cramping started.

14. Finally, patients sometimes tell us that their pregnancy is the result of rape, and while the thought of a pelvic exam and instruments in their vagina is further traumatizing, removing the pregnancy returns their body to their control.

15. I understand that Plaintiffs in this suit have asked the Court to revoke FDA's approval of Mifepristone. In my opinion, granting that request would cause overwhelming harm to patients and the medical practice. Up to 60% of abortions in the United States under 10 weeks are medication abortions, and decades of experience and an extensive body of high-quality medical literature unequivocally demonstrate that Mifepristone is safe and effective. Patients seeking medical care for their pregnancies deserve empathy and evidence-based medical care. Removing FDA approval of Mifepristone will result in delays in returning to work and family obligations, prolonged symptoms such as pain and bleeding, and an increase in surgical intervention. States with abortion bans and restrictions after the *Dobbs v. Jackson* decision are already struggling to meet the need for reproductive care for their pregnant citizens. Adding yet another barrier to safe, legal abortion care will have a harsher impact on those states, including women who must travel from those states to obtain reproductive care, and worsen the alarming disparity we see in maternal mortality, infant mortality, and childhood health outcomes. Withholding any medication that is

known to be a safe and effective treatment for the presenting problem violates the medical code of ethics and oath which medical providers swear to uphold. Mifepristone is a critical, safe, and effective step in medication abortion.

Dated: January 13, 2023

Katherine McHugh, MD

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its member organizations, their members, and these members' patients, *et al.*,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION, et al.,

Defendants.

Case No. 2:22-cv-00223-Z

PLAINTIFFS' BRIEF IN SUPPORT OF CONSOLIDATING THE PRELIMINARY INJUNCTION HEARING WITH A TRIAL ON THE MERITS UNDER RULE 65(A)(2)

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INTRODUCTION

Plaintiff medical associations, doctors, and their patients have asked this Court to enter an order, while this case proceeds, to hold the FDA to its statutory duty to protect America's women and girls from the harms of dangerous chemical abortion drugs.

For two decades, the FDA has harmed women and girls by allowing dangerous chemical abortion drugs on the market and by failing to ensure even the most basic safeguards on their use. Without regard for federal law or sound medicine, the FDA has facilitated the creation of a mail-order and online abortion economy. This suit was brought by the local emergency room doctors, OB/GYNs, and other medical professionals who have cared for an increasing number of women seeking medical attention after taking this dangerous drug regimen. For two decades, these doctors have sought to protect their patients, navigating the FDA's byzantine administrative process to challenge the FDA's actions. The FDA has stonewalled Plaintiffs at every turn, imposing bureaucratic delay after bureaucratic delay—at one point, dragging its feet for over fourteen years—just so that the FDA could try to keep the doctors out of court and avoid judicial review of its actions.

It is now far past time for the FDA to be ordered to put politics aside, follow the law, and protect America's women and girls. The best way to do so is by promptly consolidating the preliminary injunction hearing with the trial on the merits under Rule 65(a). The Court should also order the swift production of the administrative record and expedite the case for trial. This course of action will and promote judicial efficiency by avoiding briefing the same legal issues in multiple rounds before the Court. And it will enable the Court resolve this case on the merits without prejudicing Plaintiffs and without introducing further delay—delay which will result in continued harm to women and girls.

BACKGROUND

For two decades, the FDA has failed America's women and girls by allowing chemical abortion drugs on the market and by failing to require minimum safeguards on their use. Complaint, ECF No. 1 at 1–2. Plaintiff medical associations, doctors, and their patients have thus asked this Court to enter injunctive and declaratory relief against the FDA, as well as to hold unlawful, vacate, and set aside each of the FDA's actions that approved chemical abortion drugs and that removed the safeguards on their use. *Id.* at 110–11.

Before the Court is the soon-to-be complete briefing on Plaintiffs' preliminary injunction motion. Plaintiffs immediately moved for a preliminary injunction to require the FDA to withdraw or suspend each of its actions while this case proceeds. ECF No. 6, 7. The FDA and Intervenor-Defendant Danco Laboratories have now filed their opposition briefs, ECF No. 19-1, 28; Plaintiffs' reply to the FDA's opposition is due today, February 10, 2023; and Plaintiffs' reply to Danco's opposition is due February 24, 2023. The Court has yet to schedule a hearing or oral argument on Plaintiff's preliminary injunction motion.

The Court ordered the parties to submit separate briefs on whether the Court should consolidate the injunction hearing and the trial on the merits under Federal Rule of Civil Procedure 65(a)(2). ECF No. 32.

LEGAL STANDARD

Under Federal Rule of Civil Procedure 65(a), "[b]efore or after beginning the hearing on a motion for a preliminary injunction, the court may advance the trial on the merits and consolidate it with the hearing." This rule gives the district court "broad discretion in deciding whether to consolidate a preliminary injunction with the hearing of the motion for the permanent injunction." *Sonnier v. Crain*, 613 F.3d 436, 442 (5th Cir. 2010), opinion withdrawn in part on reh'g on other grounds, 634

F.3d 778 (5th Cir. 2011). "The rule permits the Trial Judge to flexibly merge and hear the component parts of a case thereby avoiding repetition and unnecessary delay." *Dillon v. Bay City Constr. Co.*, 512 F.2d 801, 804 (5th Cir. 1975). Consolidation is appropriate so long as no party shows that consolidation will cause surprise or prejudice to the party. *Nationwide Amusements, Inc. v. Nattin*, 452 F.2d 651, 652 (5th Cir. 1971).

When a court consolidates a preliminary injunction hearing with the trial on the merits, courts hear oral argument on any legal questions and hold a bench trial on evidentiary issues to resolve any factual disputes. *See, e.g.*, *Fath v. Tex. Dep't of Transp.*, 924 F.3d 132, 136 (5th Cir. 2018) (per curiam) (bench trial in APA case). The court then will "find the facts specially and state its conclusions of law separately." Fed. R. Civ. P. 52(a). The resulting hearing "really is a trial on the merits." 11A Charles Alan Wright & Arthur R. Miller, *Federal Practice and Procedure* § 2950 (3d ed. Apr. 2022 update). If there are factual issues that could "reasonably be resolved in favor of either party," then summary judgment is inappropriate, and "a finder of fact" must resolve them. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 250 (1986).

ARGUMENT

This Court should expedite decision on this case and consolidate the preliminary injunction motion with a trial on the merits under Rule 65(a). It is far past time to order the FDA to rectify its lawless approval of mifepristone and to remove chemical abortion drugs from the market, or, at a minimum, to strengthen and restore safeguards on their use.

To resolve this case promptly, and to avoid undue delay and prejudice to Plaintiffs, the Court thus should consolidate the preliminary injunction hearing with a prompt trial on the merits, stay Plaintiffs' remaining claims, immediately

direct the FDA to produce the complete administrative record, and set an expedited schedule for trial.

I. This Court should consolidate the preliminary injunction hearing with the trial on the merits.

To resolve this case quickly and efficiently, the Court should consolidate the preliminary injunction hearing with the trial on the merits under Rule 65(a).

A. This Court should bring this case to a prompt resolution on the merits.

Consolidating the preliminary injunction hearing with a final trial on the merits will avoid needless repetitive rounds of briefing and promote the prompt resolution of this case.

A prompt final judgment is in everyone's interest. Quickly disposing of a case on the merits can help plaintiffs by shortening the period of irreparable harm, can help defendants by minimizing "the potential adverse effect" of interim injunctions, and can help courts by avoiding "having the same evidence presented both at the preliminary injunction stage and later at trial." Wright & Miller, *supra*. Consolidation can also help avoid burdening the court and the parties with multiple rounds of briefing on the same dispositive legal issues. Assuming that proper notice is given in advance, this approach allows for the expedition of the case while preserving a fair opportunity for each party to raise all of its arguments, evidence, and objections at trial. *Wohlfahrt v. Mem'l Med. Ctr.*, 658 F.2d 416, 418 (5th Cir. 1981).

For three reasons, the practice of consolidation makes particular sense here. *First*, every party agrees that the outcome of this case will have far-reaching consequences for parties and non-parties nationwide, ECF No. 7 at 24–25; ECF No. 19-1 at 2, 25, ECF No. 28 at 38–40, and so everyone benefits from the certainty that

comes from avoiding interim orders and from a prompt final judgment. *Second*, this Court can ensure that, even on an expedited schedule, every party has a full and fair opportunity to present their case, including the opportunity for the FDA to present the full administrative record. *Third*, the preliminary injunction briefing raises many dispositive legal issues, and the parties have already addressed many key documents in the administrative record and the declarations. There is no need to brief the same issues on preliminary injunction motions, motions to dismiss, motions for summary judgment, and motions after trial.

In short, consolidating the preliminary injunction hearing with the trial on the merits will thus avoid needless "repetition and unnecessary delay." *Dillon v. Bay City Constr. Co.*, 512 F.2d 801, 804 (5th Cir. 1975).

B. This Court should stay Plaintiffs' other claims.

As part of consolidating the preliminary injunction hearing with the trial on the merits, this Court should hold or stay Plaintiffs' other claims or sub-claims while the Court proceeds to consider entering a partial final judgment under Rule 54(b) on the legal claims presented in the preliminary injunction motion.

Under Federal Rule of Civil Procedure 54(b), the Court may enter a partial final judgment on only certain claims in a case upon certifying that there is "no just reason for delay" of a partial final judgment on these claims. This Court can rule on the claims in the preliminary injunction motion, without reaching other claims, because there would be no just reason to delay the prompt resolution of so many dispositive claims, particularly when it may be unnecessary to ever reach Plaintiffs' additional claims.

Any claims not presented in the preliminary injunction motion thus should be stayed until after the resolution of any appeal, while reserving all rights to all

parties. The parties may notify the Court after any appeal, or when and if further litigation is necessary.

II. The Court should expedite the case, direct the FDA to immediately produce the administrative record, and set an early schedule for trial.

Consolidation need not—and should not—significantly extend the time that the FDA's actions continue to harm Plaintiff medical associations, doctors, and patients. If this Court enters an order consolidating the preliminary injunction hearing with the trial on the merits, the Court therefore should expedite this case by directing the FDA to immediately collect and produce the administrative record and by setting an expedited schedule for trial.

A. The Court should immediately direct the FDA to produce the complete administrative record.

To avoid delay and prejudice to Plaintiffs, this Court should immediately direct the FDA to collect the complete administrative record and produce it within 30 days. The Administrative Procedure Act requires a court to rule based on the complete administrative record before the agency when the decision was made. *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 420 (1971). Production of the administrative record is thus necessary for the consolidation of the preliminary injunction motion with the resolution of the merits. *See Texas v. Biden*, No. 2:21-CV-067-Z, 2021 WL 4552546, at*2 (N.D. Tex. June 7, 2021). And the parties have already attached much of the administrative record to their preliminary injunction filings.

But, in the past, the FDA has sought to avoid disclosing to the public the complete documents surrounding the agency's decisions about chemical abortion drugs. The FDA's publicly released decision documents regularly contain significant

redactions of potential important information.[1] Likewise, in response to Freedom of Information Act (FOIA) requests, the FDA has released only highly, and likely improperly, redacted versions of select documents.[2] To avoid unnecessary delay of the trial, it should be made clear at the outset that the FDA must immediately collect (and presumptively must produce) an unredacted and complete version of the administrative record for this case. *See generally Gulf Coast Rod Reel & Gun Club, Inc. v. U.S. Army Corps of Eng'rs*, No. 3:13-CV-126, 2015 WL 1883522, at *3 (S.D. Tex. April 20, 2015) (discussing circumstances when courts may order supplementation of an incomplete administrative record, such as when the agency omitted relevant evidence or documents).

Redactions may be appropriate for responses to requests for information under FOIA, but the same redactions are not appropriate in an action under the Administrative Procedure Act. After all, a "FOIA production request is an entirely discrete legal concept that bears no relation to the administrative record compiled for a court's review under the APA." *Del. Dep't of Nat. Res. & Env't Control v. U.S. Army Corp of Eng'rs*, 722 F. Supp. 2d 535, 544 (D. Del. 2010). FOIA has specific, limited exceptions to production but the administrative record under the APA "should include all materials that 'might have influenced the agency's decision.'" *La Union del Pueblo Entero v. Fed. Emergency Mgmt. Agency*, 141 F. Supp. 3d 681, 694 (S.D. Tex. 2015) (citation omitted).

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[1] *See, e.g.*, App. 517-25, 624-52.

[2] "The documents linked from this page have been redacted for certain information that is exempt from disclosure under the Freedom of Information Act, 5 U.S.C. sec. 552." http://wayback.archive-it.org/7993/20161024033540/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm085168.htm.

B. The Court should set an expedited schedule for trial.

This Court also should expedite the case and set a prompt schedule for trial.

First, this Court should set a prompt trial date. A bench trial should be held as soon as possible, but no later than two months from the court's consolidation order. An early status conference, followed by a joint pretrial report, is likely the most convenient way to identify the date, basic format, and length for the trial.

Second, this Court should enter a scheduling order setting expedited deadlines for limited supplemental briefing and for any motion practice necessary.

To allow the parties to fully develop their case, supplemental briefing should start immediately, limited to the legal claims presented in the preliminary injunction motion. Supplemental briefing should concern only issues that were not raised in the preliminary injunction motion but that are necessary for ruling on Plaintiffs' request for a partial final judgment. *See* Order, *Texas v. Biden*, No. 2:21-cv-00067 (N.D. Tex. June 29, 2021), ECF No. 66 (providing for supplemental briefing on legal standards, burdens of proof, and final remedies); Order, *Texas v. Biden*, No. 2:21-cv-00067 (N.D. Tex. July 22, 2021), ECF No. 86 (calling for supplemental briefing on final remedies). Supplemental briefing may be appropriate here, for example, on the legal standard for granting partial final judgment and on the appropriate final relief (e.g., a permanent injunction, vacatur, and a declaratory judgment) but only as to the claims present in the preliminary injunction motion. Plaintiffs' supplemental brief of up to 20 pages should be due 14 days from the Court's order; any supplemental or response briefs from the FDA and Danco Laboratories of the same lengths should be due 14 days later; and Plaintiffs' reply of up to 10 pages should be due 5 days afterward. Each party should also be allowed to submit their proposed final judgment order.

Any motions disputing the inclusion or omission of items from the administrative record, as well as any other motions raising evidentiary disputes,[3] should be expedited for decision before trial. These motions should be due within 7 days of the FDA's designation of its final production; any responses should be due 5 days later; and any replies should be due 3 days afterward.

If, after production of the final and complete administrative record, either party needs to file a supplemental brief on how new items in the administrative record bear on the issues in dispute at trial, any further supplemental briefs should be briefed on an expedited schedule for decision before trial.

Third, the Court should direct the parties to draft a joint pretrial report 20 days before trial identifying the parties' preferred format for trial, identifying any stipulations, and identifying the disputed issues of law and fact for trial. A scheduling order at or near trial can set forth appropriate deadlines for the parties to submit their post-trial proposed findings of fact and conclusions of law.

CONCLUSION

This Court should consolidate the preliminary injunction hearing with a trial on the merits under Rule 65(a)(2), stay or hold Plaintiffs' other claims, direct the FDA immediately to collect and produce the complete administrative record, and set an expedited schedule for trial.

[3] Plaintiffs do not anticipate discovery on these claims at this time, with the exception of the production of the administrative record.

Respectfully submitted February 10, 2023.

By: *s/ Julie Marie Blake*

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UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

Alliance for Hippocratic Medicine, *et al.*, Plaintiffs, *v.* U.S. Food and Drug Administration, *et al.*, Defendants.	Case No. 2:22-cv-00223-Z

Defendants' Response to Order Proposing Advancement of Trial on the Merits and Consolidation with Preliminary-Injunction Hearing

The Court has ordered the parties to brief whether a trial on the merits should be advanced and consolidated with a hearing on Plaintiffs' Motion for Preliminary Injunction under Federal Rule of Civil Procedure 65(a)(2). ECF No. 32. Defendants respectfully respond to explain why advancing a trial on the merits would be improper.

Both the Supreme Court and the Fifth Circuit have explained that accelerating a trial on the merits under Rule 65(a)(2) is "generally inappropriate." *Univ. of Tex. v. Camenisch*, 451 U.S. 390, 395 (1981); *H & W Indus., Inc. v. Formosa Plastics Corp., USA*, 860 F.2d 172, 176 (5th Cir. 1988) (quoting *Camenisch*, 451 U.S. at 395). That is especially true under the circumstances of this case. Given Plaintiffs' failure to demonstrate irreparable harm (or, indeed, *any* harm) flowing from mifepristone's[1] continued marketing, *see* Defs.' PI Opp'n (ECF No. 28) at 8-15, 31-33, coupled with their extreme delay in filing suit to challenge FDA's approval of the drug, there is no reason to decide this case on an emergency basis. Moreover, it is black-letter law that an Administrative Procedure Act (APA) case like this one must be decided not at trial, but on the basis of the full administrative record supporting the agency's decisions. In this case, there is every

[1] This brief uses "mifepristone" to refer to drug products that are approved for medical termination of early pregnancy, in both branded and generic form.

reason to follow the ordinary procedural course, including the consideration of a motion to dismiss that would narrow any issues that might need to be addressed on the merits, and thus the scope of the administrative records, which would presently span six different agency actions. Indeed, the parties' joint scheduling motion contemplated a normal briefing schedule after the conclusion of preliminary-injunction proceedings that would allow the Court to assure itself of jurisdiction before deciding the merits, *see* Joint Sched. Mot. (ECF No. 12) at 2 ("Within two weeks of this Court's ruling on Plaintiffs' [Preliminary-Injunction] Motion, the parties will propose a new answer or response deadline."), and the Court adopted that proposal, *see* Order (ECF No. 13).

Accordingly, the Court should deny Plaintiffs' preliminary-injunction motion or hold it in abeyance, then direct the parties to confer and propose within ten days a schedule for the briefing of a motion to dismiss and, if that motion is denied in whole or in part, production of the administrative records for any remaining claims and cross-motions for summary judgment.

I. Acceleration of a Determination on the Merits Under Rule 65(a)(2) Is Generally Inappropriate, and This Case Warrants No Exception.

Federal Rule of Civil Procedure 65(a)(2) provides a mechanism, in limited circumstances, for acceleration of a trial on the merits: "Before or after beginning the hearing on a motion for a preliminary injunction, the court may advance the trial on the merits and consolidate it with the hearing." But both the Supreme Court and the Fifth Circuit have cautioned that "it is generally inappropriate for a federal court at the preliminary-injunction stage to give a final judgment on the merits" using this procedure. *Camenisch*, 451 U.S. at 395; *H & W Indus.*, 860 F.2d at 176. This is because a preliminary-injunction motion is often decided in "haste" and is intended for the "limited purpose" "merely to preserve the relative positions of the parties until a trial on the merits can be held." *Camenisch*, 451 U.S. at 395. Furthermore, preliminary proceedings typically are "granted on the basis of procedures that are less formal and evidence that is less complete than in a trial on the merits." *Id*. That certainly is true in this case, where the preliminary-injunction record contains only excerpts from the underlying administrative proceedings, rather than the complete

administrative record supporting the challenged actions—multiple records spanning decades of agency decisionmaking.

As a leading treatise explains, "the Supreme Court has cautioned that although consolidation may be used to real advantage in some cases, it generally is inappropriate." 11A Charles A. Wright & Arthur R. Miller, Federal Practice & Procedure § 2590 (3d ed.). The Fifth Circuit agrees. *See, e.g.*, *H & W Indus.*, 860 F.2d at 176 (quoting *Camenisch*, 451 U.S. at 395). At a minimum, "[c]onsolidation cannot be ordered by the court without adequate notice and an opportunity for a full hearing on the merits." *Am. Fed'n of Gov't Emp., AFL-CIO, Loc. 3319, U.S. Deputy Marshals v. Colburn*, 531 F.2d 314, 315 (5th Cir. 1976); *see also, e.g.*, *Wohlfahrt v. Mem'l Med. Ctr.*, 658 F.2d 416, 418 (5th Cir. 1981) ("[S]ufficient notice is required to permit the parties to develop their cases fully.").

Consolidation under Rule 65(a)(2) may be appropriate when "a real exigency has been shown that justifies giving the case preference over other disputes that already are on the docket." 11A Charles A. Wright & Arthur R. Miller, Federal Practice & Procedure § 2590 (3d ed.); *accord Kickapoo Traditional Tribe of Tex. v. Chacon*, 46 F. Supp. 2d 644, 648-49 (W.D. Tex. 1999) (listing "exigent circumstances" as one factor to consider); *Morris v. District of Columbia*, 38 F. Supp. 3d 57, 63 (D.D.C. 2014) (same); *Zucker v. Menifee*, No. 03-cv-10077, 2004 WL 102779, at *2 (S.D.N.Y. Jan. 21, 2004) (same). Other considerations include whether "the relevant facts are undisputed," *Kickapoo Tribe*, 46 F. Supp. 2d at 648-49, and whether "[c]ombining the trial and the Rule 65(a) hearing avoids having the same evidence presented both at the preliminary injunction stage and later at trial," 11A Charles A. Wright & Arthur R. Miller, Federal Practice & Procedure § 2590 (3d ed.).

Far from warranting any exception to the general rule, this case would be particularly inappropriate for an accelerated determination on the merits. First, for the very reason that Plaintiffs fail to demonstrate irreparable harm warranting preliminary relief here, there are no "exigent circumstances" whatsoever. *Kickapoo Tribe*, 46 F. Supp. 2d at 648-49. Mifepristone was first approved nearly twenty-three years ago, yet Plaintiffs waited years to file suit to challenge its

approval. ECF No. 1, Compl. (filed Nov. 18, 2022). Even the most-recent action about which Plaintiffs complain occurred in December 2021, nearly a full year before they filed suit. In sum, given Plaintiffs' extraordinary delay in mounting this challenge, and particularly in light of their failure to demonstrate any irreparable harm (let alone irreparable harm *to themselves*) while mifepristone remains in use by other physicians, this plainly is not a case in which "a real exigency has been shown that justifies giving the case preference over other disputes that already are on the docket." 11A Charles A. Wright & Arthur R. Miller, Federal Practice & Procedure § 2590 (3d ed.); *see also* Defs.' PI Opp'n at 31-32 (collecting cases and arguing that Plaintiffs' delay undermines any claim to imminent irreparable harm).

Second, the nature of the decisions at issue further weighs against unusual expedition. Plaintiffs raise numerous theories, including novel claims second-guessing FDA's safety and efficacy determinations, and seek an order that would withdraw from the market a drug that has been widely available for more than two decades. *See* Defs.' PI Opp'n at 31 (explaining that no court has upended an FDA drug approval under similar circumstances). Although these claims lack merit for myriad reasons, including but not limited to those set forth in Defendants' preliminary-injunction opposition, ECF No. 28, the parties' arguments certainly deserve careful consideration and thorough analysis, rather than an unnecessarily rushed presentation by the parties.

Third, this is not a case where the issues are teed up through undisputed facts or where consolidation would avoid duplicative presentation of evidence at the preliminary-injunction hearing and the merits stage of the proceedings. *See Kickapoo Tribe*, 46 F. Supp. 2d at 648-49. Plaintiffs' claims arise under the APA and must therefore be decided on the full administrative records before the agency when it took the challenged actions. *See infra* Part II. Consolidating Plaintiffs' preliminary-injunction motion with a merits ruling at this time would not promote efficiency because the merits of Plaintiffs' claims are inappropriate for resolution either based on the preliminary-injunction record or through trial (or presentation of disputed facts at any stage). *See, e.g.*, *Camp v. Pitts*, 411 U.S. 138, 142 (1973) (in APA cases, "the focal point for judicial

review should be the administrative record already in existence, not some new record made initially in the reviewing court"). The case should thus proceed in the normal course, with fulsome briefing on a full record.

In sum, none of the factors that might justify deviating from the normal course of litigation and invoking Rule 65(a)(2)'s disfavored procedures is present here.

II. Accelerating a Determination on the Merits Would Substantially Prejudice Defendants.

In any event, the Court cannot properly reach the merits of the claims in this case in the absence of the full administrative record for each challenged decision. Plaintiffs' complaint presents an incomplete picture of FDA's decisions and the evidence on which they were based, including many allegations that are squarely disputed and can be evaluated only through a review of the actual, full administrative records of those decisions. *See* Compl. ¶¶ 118-254. Indeed, Plaintiffs allege that FDA's challenged actions were "unreasonable and unsupported by the evidence and information considered by the agency at the time of its decisionmaking." Compl. ¶¶ 364, 401 (challenging FDA's responses to Plaintiffs' citizen petitions); *see also, e.g.*, *id.* ¶¶ 341-44 (challenging FDA's alleged "fail[ure] to perform a statistical analysis" and "impermissibly extrapolated conclusions about the safety and effectiveness of mifepristone" when it granted approval in 2000). And even with respect to Plaintiffs' claims alleging supposed legal errors by the agency, the administrative records could provide important insight into the extent to which the agency considered and resolved such issues, and how the agency understood its overall regulatory authority in light of those issues. *See, e.g.*, *Robinson v. Veneman*, 124 F. App'x 893, 895 (5th Cir. 2005) (explaining that the "administrative record is also reviewed to determine whether the challenged action was 'contrary to constitutional right, power, privilege, or immunity'" (quoting 5 U.S.C. § 706(2)(B))). Consolidation would deprive Defendants of the opportunity to present more-fulsome briefing on such issues based on the agency's justifications in the full administrative records.

The complete administrative records are therefore an essential prerequisite to any decision on the merits by this Court. Judicial review is based upon the "full administrative record that was before [the agency] at the time [it] made [its] decision," *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 420 (1971), *abrogated on other grounds by Califano v. Saunders*, 430 U.S. 99 (1977), and "meaningful judicial review" must be based on the "agency's contemporaneous explanation" presented in the administrative record, *Department of Commerce v. New York*, 139 S. Ct. 2551, 2573 (2019). Indeed, the APA statutorily requires that any final decision on the merits be based on the full administrative record, or at least that the parties have the full record before them. *See* 5 U.S.C. § 706 ("In making the foregoing determinations, the court *shall* review the whole record or those parts of it cited by a party[.]" (emphasis added)). The record currently before the Court contains only excerpts, however, from the universe of materials that likely would constitute the full administrative records. Once compiled and certified by the agency, the complete administrative records would include additional information supporting the agency's decisions, and it is those records that must form the basis of review of these important agency actions affecting hundreds of thousands of Americans each year. Proceeding to final judgment on the merits *without* allowing Defendants to produce and present argument based on the administrative records would fall short of the process necessary to allow Defendants fully to present their case, particularly where the only briefing has taken place on a compressed preliminary-injunction timeline.

Moreover, consolidation would deprive Defendants of their ability to file a motion to dismiss raising issues that were unnecessary for resolution of Plaintiffs' preliminary-injunction motion, as anticipated by the parties' joint scheduling motion. For instance, Defendants should be afforded the opportunity to file a motion to dismiss for improper venue, on the ground that Plaintiffs have failed to establish standing for any Plaintiff located in this district. Defendants would be prejudiced by being denied the opportunity to raise such issues, given that Plaintiffs wholly failed to establish irreparable harm or to offer any legitimate basis to upend the longstanding status quo through emergency preliminary relief. And there is no reason to rush to

judgment in this case in light of Plaintiffs' extreme delay in bringing their claims, the extraordinary and unprecedented nature of the relief they seek, the absence of showing of any harm (let alone irreparable harm) to Plaintiffs, and the substantial harm that would befall physicians who prescribe, patients who use, and companies who hold the approved applications for mifepristone and could be blindsided by any ruling in Plaintiffs' favor.

III. The Court Should Deny Plaintiffs' Motion or Hold It in Abeyance, and Direct the Parties to Confer and Propose a Schedule for Further Proceedings.

Given that this is not the rare case in which invoking Rule 65(a)(2) is appropriate and that Plaintiffs have failed to show irreparable harm absent the requested extraordinary relief, this litigation should follow the ordinary procedural course: The preliminary-injunction motion should be denied or, at minimum, held in abeyance; FDA should have the opportunity to file a motion to dismiss that would narrow any issues that might need to be addressed on the merits, just as the parties contemplated in their joint scheduling proposal and the Court endorsed in its scheduling order; and, if Plaintiffs demonstrate standing to raise challenges to any agency decisions that are exhausted and not time-barred, FDA should be afforded a reasonable time to compile and certify the administrative records, and the parties should be provided an opportunity to brief cross-motions for summary judgment.

The practical importance of narrowing the scope of this case through ordinary motion-to-dismiss briefing bears emphasis here. Plaintiffs challenge no fewer than six distinct agency actions spanning more than two decades, and many of those challenges fail for threshold reasons. *See* Defs.' PI Mot. at 8-20. Thus, until this Court resolves these threshold issues—which Defendants previewed in their preliminary-injunction opposition and intend to press in more fulsome fashion in their motion to dismiss—"the time of the court should not be occupied with any further proceeding." *See United Transp. Serv. Employees of Am., CIO v. Nat'l Mediation Bd.*, 179 F.2d 446, 454 (D.C. Cir. 1949). Moreover, the potential burden on FDA of assembling administrative records for up to six discrete actions should not be underestimated. These records collectively are

likely to span tens—if not hundreds—of thousands of pages. Approximately 750 volumes of documents associated with the mifepristone new drug approval are in hard copy, nearly two-thirds of which are stored in an off-site federal record center. They must be retrieved and scanned before FDA could begin to identify precisely which documents correspond with the relevant decisions. FDA would then need to review the record documents retrieved from the archives, alongside records stored at the agency in electronic form, on a careful, page-by-page basis to redact protected information, including, for example, confidential commercial information—which FDA is bound to protect, and which it is well established does not necessarily form a part of the record for review, *see, e.g.*, *Flyers Rts. Educ. Fund, Inc. v. Fed. Aviation Admin.*, 864 F.3d 738, 745-46 (D.C. Cir. 2017); *MD Pharm., Inc. v. Drug Enforcement Admin.*, 133 F.3d 8, 13 (D.C. Cir. 1998); 21 C.F.R. § 20.61.

As a result, it will doubtless take significant time and resources to retrieve and assemble these records, an exercise that the agency reasonably has not undertaken at this preliminary stage of the case, given that the need to do so could be obviated, in whole or in part, by resolution of Defendant's threshold arguments. Narrowing the scope of this case would thus allow the agency to focus its efforts and more quickly assemble and review the records for any claims that might reach merits proceedings.

IV. A Trial Is Not Appropriate Because Plaintiffs' Claims Must Be Decided on the Administrative Record.

To the extent the Court disagrees with Defendants' position and intends nonetheless to consolidate and enter final judgment, consolidation would not warrant moving forward with a "trial on the merits," ECF No. 32, or any other judicial factfinding inquiry. This case would remain one arising under the Administrative Procedure Act, and therefore "the focal point for judicial review should be the administrative record already in existence, not some new record made initially in the reviewing court." *Camp v. Pitts*, 411 U.S. 138, 142 (1973) (per curiam); *see also*

Fla. Power & Light Co. v. Lorion, 470 U.S. 729, 743 (1985). Any contrary procedure would conflate the respective roles of the agency and the Court in APA cases.

"Under the APA, it is the role of the agency to resolve factual issues to arrive at a decision that is supported by the administrative record." *Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 13, 18 (D.D.C. 2008) (citation omitted). "[T]he district judge," in turn, "sits as an appellate tribunal," *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1083 (D.C. Cir. 2001), because "the function of the district court is to determine whether or not as a matter of law the evidence in the administrative record permitted the agency to make the decision it did." *City & Cty. of San Francisco v. United States*, 130 F.3d 873, 877 (9th Cir. 1997) (quotation omitted). "The entire case on review is a question of law, and only a question of law," *Policy & Research, LLC v. HHS*, 313 F. Supp. 3d 62, 74 (D.D.C. 2018) (quotation omitted), and "summary judgment is the proper mechanism for deciding, as a matter of law, whether an agency action is supported by the administrative record and consistent with the APA standard of review," *Lannett Co., Inc. v. FDA*, 300 F. Supp. 3d 34, 41 (D.D.C. 2017). Deciding this case at a "trial on the merits," rather than through cross-motions for summary judgment, would not only distort this Court's defined role as a court of review—rather than a finder of fact—in APA cases, but also risk exceeding the proper scope of its review, which is confined to assessing the rationality of FDA's decisions based on the record before the agency when those decisions were made. *See, e.g.*, *CTS Corp. v. EPA*, 759 F.3d 52, 64 (D.C. Cir. 2014) ("It is black-letter administrative law that in an [APA] case, a reviewing court should have before it neither more nor less information than did the agency when it made its decision."); *San Luis Obispo Mothers for Peace v. NRC*, 751 F.2d 1287, 1325 (D.C. Cir. 1986) (en banc) (noting that the record-review rule assures that, in APA cases, "the agency and not the court is the principal decision maker," and discourages courts from "cavalierly … supplement[ing] the record … in the belief that they were better informed than the administrators empowered by Congress").

Moreover, before entering any final judgment, the Court should provide the parties an opportunity to address the appropriate scope of any remedy—an issue that was not ripe for the

parties to address in their preliminary-injunction briefing, but that would be a natural part of any eventual summary-judgment briefing.

Finally, consolidation and entry of final judgment would not avoid this Court's obligation to carefully consider the equities and the public interest, since those factors would be relevant to any permanent injunction. In addition, to the extent that the Court issues an adverse judgment or injunction, the government hereby requests that any such judgment or injunction be stayed pending any appeal that is authorized and pursued. *See generally Nken v. Holder*, 556 U.S. 418, 421 (2009) ("[I]t has always been held that as part of its traditional equipment for the administration of justice, a federal court can stay the enforcement of a judgment pending the outcome of an appeal. A stay does not make time stand still, but does hold a ruling in abeyance to allow an appellate court the time necessary to review it."). The basis for this stay request is already amply set forth in Defendants' preliminary-injunction opposition, ECF No. 28 at 38-40, detailing the numerous harms that would stem from upending the status quo and abruptly withdrawing mifepristone from the market. *See, e.g.*, *Barber v. Bryant*, 833 F.3d 510, 511 (5th Cir. 2016) ("[T]he maintenance of the status quo is an important consideration in granting a stay."). At a minimum, if the Court were to enter an adverse judgment, the government respectfully requests that the Court enter a short administrative stay of 21 days to allow the government time to seek an emergency, expedited stay from the court of appeals if an appeal is authorized.

CONCLUSION

The Court should deny Plaintiffs' preliminary-injunction motion or hold it in abeyance and direct the parties to confer and propose within ten days a schedule for the briefing of a motion to dismiss and, if that motion is denied in part, production of the administrative records and cross-motions for summary judgment.

February 10, 2023

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GAO

Report to Congressional Requesters

August 2008

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex

GAO-08-751

August 2008

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex

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Highlights

Highlights of GAO-08-751, a report to congressional requesters

Why GAO Did This Study

In September 2000, the Food and Drug Administration (FDA), part of the Department of Health and Human Services (HHS), approved the drug Mifeprex for use in terminating early term pregnancy. FDA approved the drug under a provision of its Subpart H regulations, allowing it to restrict the drug's distribution to assure its safe use. Critics have questioned aspects of the Mifeprex approval process, including the reliance on historically-controlled clinical trials that compare a drug's effects on a condition to the known course of the condition rather than to another drug or placebo. Critics argued that Mifeprex does not fit within the scope of Subpart H, which applies to drugs that treat serious or life-threatening illnesses. Concerns have also been raised about FDA's oversight of the drug since approval, including the agency's response to deaths in U.S. women who had taken the drug.

In this report GAO (1) describes FDA's approval of Mifeprex, including the evidence considered and the restrictions placed on its distribution; (2) compares the Mifeprex approval process to the approval processes for other Subpart H restricted drugs; and (3) compares FDA's postmarket oversight of Mifeprex to its oversight of other Subpart H restricted drugs. GAO reviewed FDA regulations, policies, and records pertaining to its approval and oversight of Mifeprex and the eight other Subpart H restricted drugs. In addition, GAO interviewed FDA officials and external stakeholders.

To view the full product, including the scope and methodology, click on GAO-08-751. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

FDA approved Mifeprex after evaluating the sponsor's initial and revised new drug application through three review cycles. In the first cycle, FDA concluded that the available data supported the safety and efficacy of Mifeprex and that, because the course of pregnancy was well-documented and the effects of the drug were self-evident, the use of historical controls was consistent with FDA regulations. FDA also concluded that before the drug could be approved, the sponsor needed to provide final data from an ongoing U.S. trial, and more detail on restricting the drug's distribution. In the second cycle, FDA concluded that while the U.S. trial data confirmed the drug's safety and efficacy, the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In the final review, FDA concluded that termination of unwanted pregnancy is a serious condition and imposing restrictions under Subpart H was necessary. FDA approved Mifeprex, but required that the sponsor commit to conduct two postmarketing studies, imposed several distribution restrictions intended to ensure that only qualified physicians prescribe the drug, and required that patients attest to understanding the treatment's potential complications.

The approval process for Mifeprex was consistent with the processes for the other Subpart H restricted drugs, although the details of FDA's approval depended on the unique risks and benefits of each drug. Common elements of the approval processes included that FDA needed to evaluate potential limitations in key clinical data (Mifeprex and six of the other drugs), did not approve the drugs in the first review cycle (Mifeprex and five others), and imposed similar types of distribution restrictions on Mifeprex and the other drugs, though the specific details of the restrictions varied across the drugs.

FDA's postmarket oversight of Mifeprex has been consistent with its oversight of other Subpart H restricted drugs. To oversee compliance with distribution restrictions, FDA has reviewed data from all sponsors and conducted inspections for Mifeprex and two other drugs. To oversee compliance with postmarketing study commitments, FDA has relied on required updates from sponsors and found unfulfilled commitments for most drugs, including Mifeprex. To oversee compliance with adverse event reporting requirements, FDA has evaluated data in sponsors' reports and, for Mifeprex and seven other drugs, has conducted inspections that revealed deficiencies for most of these drugs, including Mifeprex. Lastly, FDA has taken similar steps to oversee postmarket safety across the drugs, such as analyzing adverse events. For Mifeprex, FDA investigated the deaths of six U.S. women who developed a severe infection after taking the drug and concluded that the evidence did not establish a causal relationship between Mifeprex and the infections. Finally, FDA has taken similar actions to address emerging safety concerns across the drugs, such as changing labeling.

HHS reviewed a draft of this report and informed GAO that it did not have comments.

Contents

Abbreviations

AERS	Adverse Event Reporting System
CDC	Centers for Disease Control and Prevention
ENL	erythema nodosum leprosum
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
HHS	Department of Health and Human Services
HIV/AIDS	human immunodeficiency virus / acquired immune deficiency syndrome
NDA	new drug application
REMS	risk evaluation and mitigation strategy
SGE	special government employee

GAO
Accountability * Integrity * Reliability

United States Government Accountability Office
Washington, DC 20548

August 7, 2008

The Honorable Michael B. Enzi
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Jim DeMint
United States Senate

The Honorable Roscoe G. Bartlett
House of Representatives

In September 2000, the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) granted marketing approval to the prescription drug Mifeprex (mifepristone) for the medical termination of early term pregnancy.[1] It remains the only drug approved in the United States for this purpose. FDA approved the drug under a provision of the agency's Subpart H regulations that allows FDA to restrict the distribution or use of a drug in order to assure its safe use.[2] Under this provision FDA can require, as it did for Mifeprex, that distribution be restricted to certain health care providers with specific training or experience. Since the drug's approval, more than 900,000 women are estimated to have taken Mifeprex in the United States.

[1]Mifeprex is the trade name for the mifepristone product marketed in the United States. Mifepristone is the name of the underlying drug substance. Mifepristone is also sometimes called "RU-486," a reference to the name the drug had during laboratory testing.

[2]Subpart H of FDA's drug approval regulations—titled "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses"—applies to drugs that are intended to treat serious or life-threatening illnesses and provide a meaningful therapeutic benefit to patients over existing treatments. The regulations contain two approval provisions. One provides a process through which FDA may restrict the distribution or use of a drug to assure its safe use. The other provides FDA with flexibilities that allow the agency to accelerate the approval process for certain drugs on the basis of clinical trial endpoints that are considered reasonably likely to predict clinical benefit. See 21 C.F.R. §§ 314.500-560 (2007).

Before a drug can be marketed in the United States, the drug sponsor must submit a new drug application (NDA) to FDA containing data demonstrating the safety and efficacy of the drug.[3] FDA reviews the NDA to determine whether the drug's benefits outweigh its risks.[4] Once FDA completes its review, the agency issues an action letter in which it either approves the drug as safe and effective for its intended use (approval letter), informs the sponsor that the drug is likely to be approved once the deficiencies FDA has identified are resolved (approvable letter), or indicates that approval cannot be obtained without substantial additional information (not approvable letter).[5] If FDA issues an approvable or not approvable letter, a subsequent review cycle can begin once the sponsor has addressed the issues FDA identified. FDA may require, as a condition of approval, that a sponsor agree to restrict the drug's distribution under the agency's Subpart H regulations.[6]

Critics have raised concerns and questions regarding several aspects of FDA's approval process for Mifeprex. For example, questions have been raised about the reliance on data from historically controlled clinical trials—trials that compare a drug's effects on a condition within the study population to the known course of that same condition in patients or

[3]A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable laws and regulations.

[4]FDA also reviews supplemental NDAs, which sponsors submit to support proposed changes to a drug's label, a new dosage or strength of the drug, a new patient population or intended use, or changes to the way the drug is manufactured after a drug has an approved NDA.

[5]FDA issued a final rule on July 10, 2008, amending its drug approval regulations. The final rule, among other things, discontinues FDA's use of approvable letters and not approvable letters. Instead, in the event that FDA determines it will not approve an application in its current form, the agency will send applicants a "complete response letter" to indicate that the review cycle for an application is complete and to describe the specific deficiencies the agency identified in the application. The amended regulations are effective on August 11, 2008. See 73 Fed. Reg. 39588-89 (July 10, 2008).

[6]21 C.F.R. § 314.520 (2007). From 1992—the year that the regulations were promulgated—through February 2007, nine drugs, including Mifeprex, had either an NDA or supplemental NDA approved under this restricted distribution provision. Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA may determine that a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks. The REMS provisions of FDAAA went into effect on March 25, 2008. As part of a REMS, FDA can require "elements to assure safe use," which include restrictions similar to those that can be required under Subpart H regulations. 21 U.S.C. § 355-1(a), (e), (f); Pub. L. No. 110-85, §§ 901, 909(a), 121 Stat. 823, 922, 926-38, 950.

populations that were not part of the trial—to support the safety and efficacy of Mifeprex.[7] FDA regulations allow for the use of such historical controls when the course of the condition in question is well-documented within a comparable population and the effect of the drug is apparent. Questions have also been raised about whether Mifeprex fit within the scope of Subpart H regulations, which apply to drugs that are intended to treat a serious or life-threatening illness. Critics have argued that unwanted pregnancy should not be considered a serious or life-threatening illness. They have also questioned whether FDA's use of Subpart H regulations was consistent with its use of the regulations to approve other drugs.

Additionally, concerns have been raised about FDA's postmarket oversight of Mifeprex, including its efforts to ensure the sponsor's compliance with conditions of approval as well as the actions the agency has taken in response to reported adverse events.[8] For approved drugs, FDA oversees sponsors' compliance with applicable reporting requirements, distribution restrictions, and other conditions of approval.[9] FDA also monitors the drugs' postmarket safety and efficacy. In the case of Mifeprex, six U.S. women have died from severe bacterial infection after taking the drug, raising questions about its safety. Some have questioned FDA's conclusion—which it discussed at a May 2006 congressional hearing—that the available evidence had not established a causal relationship between Mifeprex and the infections.

You asked us to review FDA's approval of Mifeprex and its oversight of the drug since approval. In this report we (1) examine FDA's approach to approving Mifeprex, including the types of evidence considered and the

[7]21 C.F.R. § 314.126(b)(2)(v) (2007). In contrast, clinical trials that use concurrent controls demonstrate the safety and efficacy of a drug by comparing its effects on patients in a treatment group to the effects of a different treatment—such as another drug or a placebo—on patients in a control group within the same study population.

[8]The term postmarket refers to activities occurring after a drug has been approved for marketing. FDA uses the term adverse drug event to refer to any untoward medical event associated with the use of a drug in humans.

[9]FDA regulations require sponsors of approved drugs to submit various postmarket safety reports. See 21 C.F.R. §§ 314.80, 314.81 (2007). Additionally, sponsors of approved drugs must report to FDA annually on the progress of any postmarket studies required by FDA or agreed to by the sponsor. 21 U.S.C. § 356b; 21 C.F.R. § 314.81(b)(2)(vii) (2007). FDA uses such postmarket studies to gather additional information about a drug's safety, efficacy, or use once it is marketed.

restrictions placed on its distribution and use; (2) compare the approval process for Mifeprex to the approval processes for other drugs approved under the restricted distribution provision of Subpart H; and (3) compare FDA's oversight of the use of Mifeprex since its approval to the agency's oversight of the other drugs approved under the restricted distribution provision of Subpart H.

To examine FDA's approval of Mifeprex, we reviewed relevant laws, regulations, policies, and guidance. We reviewed FDA records including an archive of documents pertaining to the approval of Mifeprex.[10] We also reviewed documentation from an FDA advisory committee meeting,[11] testimony statements and the related transcript, FDA responses to congressional requests, an August 2002 citizen's petition and responses from outside organizations, and other documentation pertaining to FDA's approval of Mifeprex. We interviewed FDA officials and external stakeholders who had access to technical information or had conducted analyses pertaining to Mifeprex that were not available through FDA. These included a representative of the sponsor of the Mifeprex application and its licensee,[12] the American College of Obstetricians and Gynecologists and the American Association of Pro Life Obstetricians and Gynecologists.

To compare the approval process for Mifeprex to those of other drugs, we reviewed FDA documentation pertaining to FDA's approval of the other eight drugs that the agency had approved under the restricted distribution

[10]In response to a Freedom of Information Act request, FDA posted certain documents pertaining to its approval of Mifeprex on the agency's Web site (see http://www.fda.gov/cder/archives/mifepristone/default.htm). The documents, which total over 9,000 pages, include a range of sometimes redacted material such as handwritten notes or email communications, communications between the drug sponsor and FDA, meeting minutes, copies of international labeling, and study protocols.

[11]FDA may convene an advisory committee to obtain advice from scientific experts and representatives of the public regarding a drug. FDA requests advice from advisory committees on a variety of matters, including aspects of drug applications and postmarket safety concerns for drug products. The primary role of an advisory committee is to provide independent advice that will contribute to the quality of the agency's regulatory decision-making. Although the committees provide recommendations to the agency, final decisions are made by FDA.

[12]The Population Council, a non-profit organization involved in reproductive health and population issues, sponsored the Mifeprex application. During the NDA review process, the Population Council contracted with Danco Laboratories, L.L.C. to serve as its licensee with responsibility for commercial manufacturing and marketing of the drug. Following the drug's approval, the Population Council transferred ownership of the Mifeprex NDA to Danco.

provision of Subpart H as of February 2007.[13] Specifically, we examined key documents related to FDA's internal review and approval processes as well as documentation from advisory committee meetings in order to identify commonalities and differences in FDA's process across the nine Subpart H restricted drugs, including Mifeprex. In our examination we focused on issues that had arisen during FDA's review of Mifeprex to determine whether similar issues had arisen in FDA's review of the other drugs, and how FDA had addressed those issues for the other drugs.

To compare FDA's oversight of the use of Mifeprex since approval to the agency's oversight of the other Subpart H restricted drugs, we reviewed relevant regulations and FDA guidance. We also examined FDA documentation on the agency's oversight of sponsors' compliance with distribution restrictions, postmarketing study commitments, and adverse event reporting requirements for the nine Subpart H restricted drugs. In addition, we reviewed FDA's process for evaluating and responding to postmarket data on adverse events for each drug. Lastly, we interviewed FDA officials and staff who are responsible for postmarket oversight of these drugs. We conducted our work from February 2007 through August 2008 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Results in Brief

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of its Subpart H regulations after examining the NDA through three review cycles. In its first review, FDA concluded that the available evidence supported the safety and efficacy of Mifeprex. This conclusion was based in part on FDA's determination that because the course of pregnancy was well-documented and the effects of the treatment were self-evident, the reliance on historical controls in three key clinical trials—two conducted in France and one ongoing in the United States—was appropriate and consistent with FDA regulations. FDA issued an approvable letter in September 1996 concluding that the sponsor needed

[13]We initiated our work in February 2007. In June 2007, FDA approved one additional drug—Letairis—under the restricted distribution provision of Subpart H. This drug was not included in our review.

to provide additional information, such as the final data from the U.S. trial and a detailed plan to restrict the drug's distribution, before an approval decision could be made. The second review cycle began when the sponsor submitted a complete response to this letter. FDA issued a second approvable letter in February 2000 after concluding that the new data confirmed the safety and efficacy of Mifeprex for the U.S. market but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In its final review, FDA deliberated about the distribution restrictions and conditions of use needed to assure the safe use of the drug. FDA concluded that termination of an unwanted pregnancy is a serious condition and that the drug can allow patients to avoid a surgical procedure and therefore Mifeprex fit within the scope of Subpart H. FDA further concluded that the drug could only be used safely if distribution was limited to qualified physicians. The sponsor argued that the drug did not treat a serious condition and that because they had voluntarily agreed to the restrictions FDA had requested, it was neither appropriate nor necessary to impose the restrictions under Subpart H. However, the sponsor eventually acquiesced to FDA's requirement that approval be under Subpart H. After FDA concluded that the sponsor had adequately revised its distribution plan and addressed the remaining issues identified in FDA's reviews, it approved the Mifeprex NDA under Subpart H with several restrictions. These included requiring that prescribing physicians attest to possessing specific skills, agree to fully discuss the treatment with patients, and agree to report certain adverse events to the sponsor; that the drug be distributed directly to physicians by an authorized distributor; and that patients attest to fully understanding the treatment and its potential complications. The drug was also approved subject to the sponsor's commitment to conduct two postmarket studies related to patient outcomes.

The approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs, but the details of FDA's approval process for each drug depended on the drug's unique risks and benefits. One common element across the approval processes for seven of the drugs, including Mifeprex, was that FDA needed to evaluate potential limitations—such as lack of concurrent controls or small sample sizes—in key clinical trials supporting the NDA. For some of these drugs other than Mifeprex, FDA concluded that there were weaknesses in the data submitted in the NDA that needed to be addressed. Another common element for six of the drugs, including Mifeprex, was that FDA issued at least one prior action letter before ultimately approving the drug for marketing under Subpart H. Additionally, the types of distribution restrictions that FDA imposed on Mifeprex were similar to

those the agency imposed on the other drugs, though the details of the restrictions varied depending on the drug. Lastly, eight of the drugs, including Mifeprex, were approved with two or more postmarketing study commitments, each with one or more commitments related to adverse events or patient outcomes of interest.

FDA's postmarket oversight of Mifeprex has been consistent with the agency's postmarket oversight of the other Subpart H restricted drugs. To oversee the drug sponsors' compliance with distribution restrictions, FDA has relied on data submitted by sponsors for all of the drugs. For three of the drugs, one of them Mifeprex, FDA has also completed inspections of the sponsor or its distributors. To oversee compliance with postmarketing study commitments, FDA has relied on updates in required reports from sponsors. Most of the drugs, including Mifeprex, have at least one study commitment that remains unfulfilled. To oversee compliance with adverse event reporting requirements, FDA has relied on sponsors' reports for all of the drugs and has also conducted inspections of the sponsor or its manufacturers for eight of them. FDA has cited the sponsors of seven of the drugs, including Mifeprex, for adverse event reporting deficiencies. To oversee the postmarket safety of all of the Subpart H restricted drugs, FDA has routinely conducted reviews of adverse event reports to monitor for safety concerns. In the case of Mifeprex, FDA investigated the deaths of six U.S. women who developed a fatal infection following treatment with Mifeprex for medical abortion. FDA has determined that in all six of the deaths, the women used a Mifeprex treatment regimen that has not been approved by FDA. Based on its investigations, FDA has concluded that a causal relationship between the use of Mifeprex and the fatal infections has not been established. FDA has also monitored other kinds of adverse events and has concluded that, with the exception of the cases of fatal infection, reported serious adverse events associated with Mifeprex have been within or below the ranges it expected. Additionally, for Mifeprex and the other drugs, FDA has taken similar actions—such as issuing warnings and requesting changes to the product labeling—to communicate safety information to consumers and health care providers.

HHS reviewed a draft of this report and informed us that it did not have general comments. In addition, HHS provided technical comments which we incorporated as appropriate.

Background

The Mifeprex NDA provided for the use of Mifeprex, in combination with another drug, for the medical termination of pregnancy. The treatment regimen described in the NDA involved taking Mifeprex orally, and then taking the drug misoprostol orally 2 days later unless termination of the pregnancy had already occurred.[14] Patients return for a follow-up visit with their prescribing physician 2 weeks later to ensure that the termination of the pregnancy has been completed. The treatment regimen works by both interrupting the hormones that the body needs to maintain a pregnancy and inducing the uterine cramping necessary to cause a medical abortion.

At the time that the drug sponsor submitted the Mifeprex NDA, in March 1996, mifepristone had already been approved in multiple countries. The drug was first approved for the medical termination of pregnancy in France and China in 1988.[15] It was approved subsequently in the United Kingdom in 1991, in Sweden in 1992, and various other European countries throughout the 1990s. In general, the treatment regimens approved in these countries were similar to those studied in the Mifeprex NDA, though in some cases the specific drug used in combination with mifepristone was different.

FDA Application Review Process

FDA reviews drug applications to determine whether they provide sufficient evidence to demonstrate that a drug is safe and effective for the proposed use, including whether the benefits of the drug outweigh its risks. FDA's formal process for new drug approval begins after a drug sponsor submits an application, typically following a long period of research and development. During a preliminary review, FDA determines whether the application is sufficiently complete to be reviewed and if so, designates it for either standard or priority review, depending on the

[14]Misoprostol is one of several drugs that had been studied in combination with mifepristone for the medical termination of pregnancy because they have been shown to induce uterine contractions. However, it is approved for marketing in the United States for a different indicated use.

[15]The company that discovered mifepristone and manufactured it for marketing in France—Roussel Uclaf—did not want to produce the drug for the U.S. market. Instead, the U.S. sponsor retained a contract manufacturer. For a more detailed discussion of the history of the development of mifepristone for the U.S. market, see: Congressional Research Service, *Abortion: Termination of Early Pregnancy with RU-486 (Mifepristone)*, (Washington, D.C.: 2001).

therapeutic potential of the drug.[16] The agency then assigns a team of reviewers—including medical officers, chemists, statisticians, microbiologists, pharmacologists, and other experts—within the relevant FDA review division. This review team, which is usually led by a medical officer, conducts a comprehensive evaluation of the clinical and non-clinical information in the application including the safety and efficacy data for the drug, the design and quality of the studies used to support the application, and the proposed labeling for the drug and also reviews the results of inspections of the facilities where the drug is manufactured.[17] The review team compiles the results of its analyses and recommends either an approval, approvable, or not approvable action.

FDA managers, usually including the review team's supervisor and senior management within the applicable review division, determine what action to take on an application, based on the recommendations of the review team. These managers examine the review team's analysis and individually decide whether to concur with the recommendation. The final decision on the action the agency should take is usually, but not always, made by the director of the applicable review division. In some cases, actions must be reviewed and agreed to by the relevant FDA office.

This review process may span several cycles. For those applications not approved during the first review cycle—both approvable and not approvable—the second FDA review cycle begins once the sponsor submits an amendment to the application providing responses to the deficiencies FDA identified in its previous review. These amendments often contain additional studies, analyses, data, or clarifying information to address FDA's concerns. The responsible review team reviews the information provided by the sponsor, conducts any additional analyses that are required, reviews the results of any additional inspections that have been conducted, and again recommends either an approval, approvable, or not approvable action. As with the first review cycle, the process ends once FDA management reviews the recommendations of the

[16]FDA may grant priority review status when it determines that a drug may provide significant benefits in the treatment, diagnosis, or prevention of a disease as compared to marketed drugs or non-drug therapies, such as surgery, or provide a treatment where no adequate therapy exists.

[17]The non-clinical data in an NDA pertains to, for example a drug's chemistry, manufacturing, and controls as well as its toxicology and pharmacology.

review team and makes its decision on the action to take on the application.

Restricting Drug Distribution and Subpart H Regulations

To address concerns FDA identifies regarding the safe use of a drug, the agency may condition approval by requiring that the sponsor agree to restrict the drug's distribution. FDA has established restricted distribution programs for approved drugs primarily by requiring that a drug's approval be under the restricted distribution provision of Subpart H regulations. According to the scope of the regulations, Subpart H applies to new drugs that "have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments" for the condition.[18] FDA may approve a drug under the restricted distribution provision of these regulations if it meets these criteria and the agency concludes that the drug is effective but can be safely used only if distribution or use is restricted. For example, FDA may require that distribution of a drug be limited to certain facilities or physicians with special training.

As of February 2007, nine drugs—Actiq, Accutane, Lotronex, Mifeprex, Plenaxis, Revlimid, Thalomid, Tracleer, and Xyrem—had either an NDA or supplemental NDA approved under the restricted distribution provision of Subpart H.[19] For each of the drugs, either during the application review process or based on postmarket data, FDA identified concerns about the safe use of the drug that led the agency to apply Subpart H. The drugs were approved to treat a range of conditions, such as breakthrough cancer pain, specific symptoms of narcolepsy, and severe acne.

FDA has also required that drug sponsors agree to restrict the distribution of drugs without imposing Subpart H. Clozaril, Tikosyn, and Trovan are three examples of drugs that have restricted distribution programs that were imposed outside of Subpart H. (See app. I for a table describing drugs FDA has approved with restricted distribution programs and the conditions they are intended to treat). While Clozaril was first approved in

[18]21 C.F.R. § 314.500 (2007).

[19]21 C.F.R. § 314.520 (2007). The sponsor for Plenaxis—approved in 2003 for the palliative care of certain patients with advanced prostate cancer—withdrew the product from the market in 2006. Additionally, three generic versions of Accutane have been approved for marketing under this restricted distribution provision.

1989, FDA imposed distribution restrictions on both Tikosyn and Trovan after Subpart H regulations had been promulgated.

A second approval provision of Subpart H provides FDA with flexibilities that allow the agency to accelerate the approval process for drugs that provide meaningful therapeutic benefits over alternatives for serious or life-threatening illnesses.[20] Specifically, under the provision, FDA may approve a drug on the basis of clinical trials establishing that the drug has an effect on a surrogate endpoint—such as weight gain or reduced occurrence of infections in patients with HIV—that is reasonably likely to predict a clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.[21] This allows FDA to approve a drug before measures of effectiveness that would usually be required for approval are available. However, under this approval provision, drug sponsors are ordinarily required to conduct postmarket studies to confirm and further describe the drug's clinical benefit. As of February 2007, FDA had used this provision to approve 52 drugs, most of which are intended to treat HIV/AIDS or various cancers.

FDA's Role in Postmarket Oversight

Because some risks may not become known until after a drug's approval and use in a wider segment of the population, FDA has a range of postmarket oversight responsibilities once a drug is approved for marketing in the United States. FDA's postmarket oversight responsibilities include assessing sponsors' compliance with requirements for a given drug, such as postmarketing study commitments, adverse event reporting, and restricted distribution requirements. In addition, FDA monitors reported adverse events to assess the postmarket safety of approved drugs and may take action if it develops a concern about a drug's safety.

With regard to postmarketing study commitments, FDA oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report to FDA annually on their progress in meeting the

[20]See 21 C.F.R. § 314.510 (2007).

[21]According to FDA, although some surrogate endpoints are recognized as well-established and have long been a basis for approval (such as change in blood pressure or cholesterol), accelerated approval regulations allow reliance on a "surrogate endpoint that, while 'reasonably likely' to predict clinical benefit, is not so well-established as the surrogates ordinarily used as bases of approval in the past." 57 Fed. Reg. 58942, 58944 (Dec. 11, 1992).

commitments. FDA requires that sponsors report on the status of these studies in an annual report that also includes updates on the distribution of the drug, labeling changes, clinical literature published on the drug, and the drug's marketing.[22] FDA designates unfulfilled study commitments as submitted, pending, ongoing, delayed, released, or terminated.

FDA also oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report periodically to FDA on safety information and specific types of adverse events that occur in association with an approved drug.[23] Sponsors must provide in periodic reports (quarterly for the first 3 years after approval and annually thereafter) a narrative summary and analysis of adverse event information. For adverse events that are considered both serious and unexpected,[24] sponsors are required to submit a report—known as a "Postmarketing 15-day Alert Report"—to FDA within 15 calendar days from the time the sponsor was informed of the event. To assess sponsors' compliance with these adverse event reporting requirements, FDA reviews sponsors' reports and conducts inspections of the sponsors' reporting policies and procedures.

For drugs approved under the restricted distribution provision of Subpart H, FDA oversees sponsors' compliance with the restrictions placed on the drugs' distribution or use. To assess compliance with restrictions, FDA reviews information such as summaries of sponsors' distribution programs in annual reports and in some cases separate reports required by the agency to provide details and updates on distribution programs. In addition, FDA may conduct inspections of a sponsor's corporate headquarters, manufacturing sites, or contractors, such as specialty distributors, to evaluate whether distribution policies and procedures comply with the approved restrictions for a given drug. If FDA identifies deficiencies during an inspection, it may issue a formal citation—known as a Form FDA 483. In addition, FDA may communicate less serious findings as written or oral "observations" or "recommendations."[25]

[22]See 21 C.F.R. § 314.81 (2007).

[23]See 21 C.F.R. § 314.80 (2007).

[24]Unexpected events are those that are not included in the current labeling for a drug.

[25]FDA uses the same reporting scheme—noting citations, observations, or recommendations— for its inspections to assess sponsor compliance with adverse event reporting.

To monitor postmarket safety of approved drugs, FDA reviews clinical literature, routinely evaluates the available data on reported adverse events, and conducts investigations of the nature and patterns of these events. FDA compiles data from sponsor's reports on adverse events, along with data from voluntary reports submitted to the MedWatch program, in its Adverse Event Reporting System (AERS) database.[26] FDA safety evaluators analyze data from AERS and in the clinical literature to detect signs of potential safety concerns. These evaluations may reveal the need for further studies of a drug or may result in FDA action to ensure the safety of the drug.[27]

If FDA identifies problems with a sponsor's compliance with agency requirements or identifies postmarket safety concerns, the agency can take a range of actions to address the concern and communicate safety information to healthcare providers and the public. For example, FDA may revise the restrictions on a drug's distribution, request changes to a drug's labeling, issue patient advisories or public health alerts, or request that a sponsor issue letters to health care providers or pharmacists to alert them to safety concerns. FDA may also issue a regulatory letter citing violations of laws or regulations. Typically, FDA issues a Warning letter for violations that may lead FDA to pursue further enforcement action if not corrected or issues an untitled letter for violations that do not meet this threshold. FDA also has the authority to withdraw a drug's marketing approval for safety-related and other reasons,[28] although it rarely does so. Additionally,

[26]MedWatch is a voluntary reporting program through which health professionals and consumers can report adverse reactions, product problems, and use errors related to drugs and other products approved by FDA.

[27]GAO has previously reported on and made recommendations regarding FDA's postmarket oversight of approved drugs. See GAO, *Drug Safety: Improvements Needed in FDA's Postmarket Decision-making and Oversight Process*. GAO-06-402. (Washington, D.C.: Mar. 31, 2006).

[28]21 U.S.C. § 355(e).

Subpart H regulations establish an expedited process for withdrawing a drug's marketing approval, in certain circumstances.[29]

FDA Approved Mifeprex under the Subpart H Restricted Distribution Provision After Concluding That Clinical Evidence Supported Its Safety and Efficacy

FDA approved Mifeprex after three review cycles. In its initial review, FDA concluded that reliance on historical controls in three key clinical trials was appropriate and consistent with FDA regulations and that the available data supported the safety and efficacy of the drug. In an approvable letter, FDA notified the sponsor that it needed to provide additional data and more detail on its proposal to restrict the drug's distribution before an approval decision could be made. A second review cycle began when the sponsor submitted data responding to this letter. The agency issued a second approvable letter after finding that new data confirmed Mifeprex's safety and efficacy but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. FDA further concluded that the drug was a candidate for approval under Subpart H. In the final review cycle, FDA concluded that the sponsor's revised distribution plan and other revisions were sufficient to address FDA's comments. FDA also concluded that Mifeprex met the scope of Subpart H and that approval under the restricted distribution provision of Subpart H was necessary to ensure that only qualified physicians prescribed the drug. On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of Subpart H with several restrictions and two postmarketing study commitments. (See table 1 for a timeline of key events in the Mifeprex approval process.)

[29]Under Subpart H regulations, FDA may withdraw a drug's marketing approval after providing for a hearing, in the following circumstances; (1) a postmarketing clinical study fails to verify clinical benefit; (2) the sponsor fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product; (4) the sponsor fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use. 21 C.F.R. § 314.530 (2007).

Table 1: Timeline of Key Events in FDA's Approval of Mifeprex

Date	Event
First review cycle	
March 1996	The sponsor submitted a new drug application (NDA) for the use of Mifeprex in combination with the drug misoprostol for the medical termination of intrauterine pregnancy.
July 1996	FDA Reproductive Health Drugs Advisory Committee meeting.
September 1996	FDA issued an approvable letter listing issues that the sponsor needed to address before the application could be approved.
Second review cycle	
August 1999	After delays securing a manufacturer, the sponsor completed its responses to FDA's 1996 approvable letter.
February 2000	FDA issued a second approvable letter, listing issues that the sponsor needed to address prior to approval.
Third review cycle	
March 2000	The sponsor completes its responses to FDA's second approvable letter.
September 2000	FDA approved Mifeprex under the restricted distribution provision of Subpart H.
November 2000	Distribution of Mifeprex began in the United States.

Source: GAO analysis of FDA and drug sponsor data.

FDA's Initial Review Cycle and Approvable Action (March to September 1996)

FDA's initial review began when the drug sponsor submitted the Mifeprex NDA in March 1996. After conducting a preliminary review of the NDA, FDA designated the application for priority review, establishing a goal that the agency would issue an action letter within 6 months. FDA's rationale for the designation was that as the first drug that would be approved for its particular indication, Mifeprex was a therapeutic advance because women using the drug could potentially avoid the risks of surgery and anesthesia involved in a surgical termination of a pregnancy.

FDA assigned a team of reviewers within the Division of Reproductive and Urologic Drug Products to review the evidence in the Mifeprex NDA. The key safety and efficacy data in the NDA consisted of three historically controlled clinical trials, two conducted in France and one conducted in the United States. These trials studied the Mifeprex treatment regimen—mifepristone in combination with misoprostol—in a total of more than 4,000 women. At the time the NDA was submitted, the French trials were complete and the U.S. trial was ongoing. As a result, during the first review cycle, the review team analyzed the complete safety and efficacy data from the French clinical trials, but only summary data on serious adverse events

from the U.S. clinical trial. FDA reviewers also considered results from other trials conducted in Europe from 1983 through 1996 in which mifepristone was studied either alone or in combination with misoprostol or similar drugs. In addition, the review team considered safety information from extensive postmarketing experience in Europe, including a postmarket safety database containing information on women who had used mifepristone. Lastly, the review team considered the non-clinical data in the application, including data on the drug's chemistry and manufacturing.

In its review of the Mifeprex data, FDA reviewers determined that the reliance on historical controls in the key clinical trials was appropriate and consistent with FDA regulation. According to FDA, historical control designs can make it more difficult to evaluate which effects can be attributed to the drug being studied.[30] However, FDA regulations list historical controls as an acceptable type of control when the natural history of the condition being treated is well-documented and when the effects of the drug are self-evident.[31] In the case of the Mifeprex NDA, FDA determined that the historically controlled trials provided substantial evidence of safety and efficacy because the outcomes of women taking the Mifeprex regimen were compared with the well-documented data on the natural course of pregnancy, including rates of miscarriage, and the effect of the drug—termination of a pregnancy—was obvious.[32]

To assist the review team in its assessment of Mifeprex, FDA convened the Reproductive Health Drugs Advisory Committee in July 1996 and asked the members to examine the data and vote on their conclusions regarding the drug's safety and efficacy. Six of the eight voting members voted, with

[30]See FDA, *Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Tials* (Rockville, Md.: May 2001).

[31]21 C.F.R. § 314.126(b)(2)(v) (2007). The regulation also states that studies that are "adequate and well-controlled" provide the primary basis for determining whether there is "substantial evidence" in support of the claims of effectiveness for new drugs. Among other things, an adequate and well-controlled study provides sufficient details of study design, conduct, and analysis to allow critical evaluation, and the design must permit a valid comparison with a control to provide a quantitative assessment of the drug's effect.

[32]FDA has cited examples of other drugs that have relied upon historical controls. According to FDA, for contraceptives the effect of the drug can be compared to the well-documented rate of pregnancy in sexually active women between the ages of 15 and 35 in the absence of contraception. For example, FDA approved the contraceptive drug products Lybrel, Implanon, Yaz, and NuvaRing on the basis of historically controlled clinical trials.

two abstentions, that the available evidence demonstrated that the benefits of the regimen outweighed its risks for the proposed indication in the United States. However, the members agreed unanimously that FDA should provide the final safety and efficacy data from the U.S. clinical trial for their review. The advisory committee also discussed the basic elements of a voluntary restricted distribution system proposed by the drug's sponsor, which would require that Mifeprex be distributed directly to physicians, that prescribing physicians meet certain training requirements, and that patients meet certain conditions before receiving the drug. The advisory committee voted unanimously that they agreed with the concept of restricting distribution of the drug but had reservations about how the proposed system would assure that physicians had adequate credentials. The members recommended that the sponsor conduct postmarket studies to address six unanswered questions about the treatment regimen and the distribution system. The members also provided extensive comments on the draft labeling proposed by the sponsor.

The FDA review team concluded that the NDA was approvable, based on its assessment of the clinical and non-clinical data and the input from the advisory committee. The medical officer leading the review team concluded that the available clinical data indicated "that medical abortion can be safely delivered in a wide variety of United States settings." The data from the French trials showed the treatment to be roughly 95 percent effective at terminating pregnancy through 49 days gestation. The data from the French clinical trials also showed that almost all patients experienced some side effects—such as uterine cramping and bleeding—most of which were expected based on the way the drug works. Though serious adverse events were considered rare, some women experienced bleeding that required medical intervention, and approximately 0.2 percent of patients required transfusion. The medical officer concluded that the preliminary U.S. data on adverse events did not appear to differ significantly from the French trials.[33]

[33]The medical officer noted that it was only possible to make general comparisons across these events because definitions and reporting requirements were different in the two countries. Additionally, while the sponsor had not yet completed its analysis of the safety and efficacy data from the U.S. clinical trial, information from the studies was forwarded to the sponsor weekly. The medical officer concluded, based on preliminary examination of this information, that the final results of the U.S. trials were likely to be similar to the results of the French trials.

In September 1996, FDA issued an approvable letter for the use of Mifeprex in combination with the drug misoprostol for the termination of intrauterine pregnancy up to 49 days gestation. In memos documenting concurrence with the review team, and in the approvable letter itself, FDA management outlined the clinical and non-clinical issues the sponsor needed to address prior to approval. First, the full data from the U.S. clinical trial were needed to establish safety and efficacy of the Mifeprex regimen in the U.S. health care setting. Second, FDA agreed with the sponsor's proposal to limit the drug's distribution, but the sponsor had not yet submitted sufficient detail on how it would be implemented to allow for the plan to be fully evaluated.[34] Third, the drug labeling proposed by the sponsor needed to be revised to provide more information on the treatment and to address comments from the advisory committee. Fourth, the sponsor would need to commit to pursue the postmarket studies suggested by the advisory committee. Finally, the sponsor would need to address certain deficiencies in chemistry and manufacturing data identified in FDA's review.

FDA's Second Review Cycle and Approvable Action (August 1999 to February 2000)

FDA's second review cycle for the Mifeprex NDA officially began once the sponsor had completed its responses to the first approvable letter. However, these responses were delayed because of difficulties the sponsor encountered in securing a manufacturer for the drug product. In the interim, the sponsor submitted a range of data to FDA, including the final safety and efficacy results from the U.S. clinical trial, updated safety data from other trials of mifepristone and international postmarketing experience with the drug, formal revisions of the product labeling, and outstanding chemistry and manufacturing data. In August 1999, the sponsor completed its responses to the approvable letter by submitting an overview of the key principles of the restricted distribution system as well as responses to the postmarketing study commitments. At the time of this submission, the sponsor was still working with its planned distributor on the details of the restricted distribution system.

Based on the updated data, the review team recommended approval for the Mifeprex NDA once the sponsor had clarified the details of the drug's distribution, revised the drug labeling, and addressed deficiencies in the

[34]FDA management's concurrence memos noted that because the sponsor had voluntarily proposed a restricted distribution system, imposing restrictions through Subpart H regulations did not appear warranted.

chemistry and manufacturing data. The medical officer concluded that the final results from the U.S. clinical trial were acceptable and confirmed the results of the French trials that the regimen was safe and effective.[35] The medical officer concluded that the comments from the July 1996 advisory committee meeting were fully considered and, to the extent possible, implemented.[36] The medical officer also concluded that additional detail was needed to determine whether the sponsor's proposed distribution plan was sufficient. The non-clinical reviews during this review cycle—which included inspections of manufacturing facilities[37]—identified deficiencies in the drug's chemistry data and manufacturing processes that needed to be addressed, as well as sections of the drug's labeling that needed to be revised.

In January 2000, the sponsor submitted a more detailed plan describing how the proposed distribution restrictions would be implemented. The plan had three key elements. First, the Mifeprex regimen would only be administered under the supervision of qualified physicians who had agreed to provide the treatment according to several guidelines. Specifically, prescribing physicians would be required to attest to being able to accurately assess the duration of a pregnancy, diagnose an ectopic pregnancy,[38] and assure that patients have access to appropriate follow up care if needed to manage complications. The physicians would also need to agree to fully explain the procedure to each patient and obtain her

[35]The U.S. clinical trial data showed the treatment to be 92 percent effective for terminating pregnancy through 49 days gestation, which was slightly lower than the 95 percent from the French trials. Adverse event rates were also slightly higher in the U.S. trials. The medical officer attributed these differences to the relative inexperience of U.S. clinicians with the treatment. In addition, the medical officer concluded that the updated information from international studies, postmarket experience, and the published literature was consistent with the results from the U.S. and French trials.

[36]In November 1999, FDA provided advisory committee members the final results from the U.S. clinical trial for their review and comment. FDA did not receive any comments from the members on these results.

[37]The drug substance (mifepristone) in the Mifeprex product was manufactured by the Shanghai Haulian Pharmaceutical Co., Ltd., with the manufacturing facilities located in China. Initial FDA inspections found the manufacturer not in compliance with FDA's good manufacturing practice standards.

[38]Ectopic pregnancy—which occurs when a fertilized egg improperly implants outside of the uterus—is a contraindication for receiving the Mifeprex regimen. Accurate screening to ensure that patients with an ectopic pregnancy do not receive the treatment was a concern because a ruptured ectopic pregnancy is a life-threatening condition and its symptoms are similar to the side effects of the Mifeprex regimen.

signed consent, record the unique product serial number for tracking purposes, and report any serious adverse event or on-going pregnancy to the sponsor. Second, the drug would only be distributed directly to physicians after an authorized distributor had verified that the physician had registered with it and had a signed attestation on file. Third, patients would be required to meet certain conditions before receiving the drug, such as signing a patient agreement attesting to her understanding of the potential complications of the treatment.

FDA management concluded that the proposed distribution plan did not provide for adequate training and certification of prescribing physicians and needed to be revised before the NDA could be approved. In February 2000, FDA issued a second approvable letter for Mifeprex, notifying the sponsor that it needed to revise its proposed distribution plan, address deficiencies in the drug's chemistry data and manufacturing, and revise the drug's labeling. The letter also stated that FDA had considered the application under the restricted distribution provision of Subpart H and that distribution restrictions would be necessary in order to assure the safe use of the drug. The approvable letter further reminded the sponsor of its commitment to pursue postmarketing study commitments to address questions that were raised at the time of the advisory committee meeting.

FDA's Final Review Cycle and Marketing Approval for Mifeprex (March to September 2000)

In March 2000, the sponsor submitted its complete response to FDA's February 2000 approvable letter. This submission included updated safety data from ongoing trials and international postmarket experience, international product labeling, and revisions to the distribution plan. The sponsor also provided additional data and revisions—including updated chemistry and manufacturing data, a revision to the distribution plan, and revised labeling—to address comments from FDA that arose during the review cycle. The agency's review of these submissions included multiple meetings and teleconferences with the sponsor and input from a consultant who was a special government employee (SGE) and a member of the Reproductive Health Drugs Advisory Committee.[39]

[39]According to FDA, it is not uncommon for the agency to consult with members of its advisory committees who have special expertise in a particular drug under review. Generally, an SGE is defined as an officer or employee who is retained, designated, appointed, or employed by the government to perform temporary duties, with or without compensation, for not more than 130 days during any period of 365 consecutive days. 18 U.S.C. § 202(a).

During the final review cycle, FDA's deliberations—which involved a wide range of agency staff and management, including at times the Commissioner—focused on four key issues: whether prescribing physicians should be required to participate in a formal training and certification program, whether to require that approval be under Subpart H, what conditions of use should be specified, and what postmarketing study commitments would be needed to assure the safe use of the drug.

- Physician Training: In its deliberations, FDA considered requiring that physicians participate in specific training and have their qualifications certified before being allowed to prescribe Mifeprex, as opposed to relying on the sponsor's proposed system of self-attestation. However, FDA concluded that such a requirement was not necessary. FDA officials told us that the agency determined that its concern about ensuring that prescribers were adequately qualified could be addressed by requiring that the sponsor make educational materials and training programs readily available and requiring that prescribing physicians sign an agreement attesting to their qualifications. The SGE consultant agreed with this conclusion. FDA officials also told us that the agency wanted to minimize the burden that the restricted distribution program would place on providers and patients by requiring only what was necessary to address safety concerns.[40]

  In July 2000, the sponsor submitted its revised distribution plan. This plan addressed FDA's comments by providing increased emphasis in the product labeling on the educational materials and trainings available to physicians and the importance of participating in the training. The other key elements of the plan—including the specific qualifications that physicians were required to meet and agreements regarding discussing the treatment and adverse event reporting—were essentially unchanged from those the sponsor proposed in its January 2000 plan.

- Approval under Subpart H Regulations: FDA had maintained through the first two review cycles that distribution restrictions would be required for Mifeprex. However, minutes from meetings between FDA and the sponsor indicate that the agency was still considering whether it was necessary to impose those restrictions under Subpart H during the final review cycle. During the second review cycle, FDA had concluded that the restricted

[40]Subpart H regulations state that any restrictions imposed will be commensurate with the specific safety concerns presented by the drug product. 21 C.F.R. § 314.520(b) (2007).

distribution provision could be applied to Mifeprex.[41] FDA eventually concluded that it would be necessary to do so. In its documented rationale for this conclusion, FDA stated that the drug met the scope of the regulations because the termination of an unwanted pregnancy is a serious condition, and that the drug provided a meaningful therapeutic benefit over existing therapies by allowing patients to avoid the procedure required with surgical termination of pregnancy. FDA officials told us that the agency has broad discretion to determine which conditions or illnesses may be considered serious or life threatening, and that in the case of Mifeprex it considered the potential in any pregnancy for serious or life-threatening complications—such as hemorrhage—in its determination.[42] Additionally, FDA concluded that Mifeprex could only be used safely if distribution was limited to physicians who could assess the duration of a pregnancy, diagnose an ectopic pregnancy, and provide patients with access to surgical intervention if necessary.

Throughout the approval process, the sponsor was opposed to approval under Subpart H. Specifically, the sponsor argued that the drug did not fit within the scope of Subpart H because pregnancy itself is not a serious or life threatening illness. The sponsor also argued that the intent of the restricted distribution provision was to allow for restricted distribution of highly toxic or risky drugs, and that Mifeprex did not fit this description.[43] The sponsor also expressed concern that approving the drug under Subpart H could unfairly mark Mifeprex as risky and deter women from using the drug. Lastly, the sponsor held that imposing Subpart H was unnecessary because it had voluntarily committed to the distribution

[41]FDA had also noted that approving the drug under Subpart H would allow the agency to impose similar restrictions on any future generic mifepristone products approved for the same indication. The patent for Mifeprex expired in October 2004, but as of May 2008, no generic versions of mifepristone have been approved for marketing.

[42]The terms "serious" and "life-threatening" are not defined in Subpart H regulations, but were discussed in the preambles to the proposed and final rules. In its proposed rule, FDA stated that the seriousness of a disease is a matter of judgment, but generally is based on its impact on survival, day-to-day functioning, or other factors, and provided examples of conditions that could be within the scope of the regulation. FDA noted that many diseases or conditions can be serious for some populations in some or all of their phases and explicitly reserved the discretion to determine whether the regulations were applicable to a given product. See 57 Fed. Reg. 13234-5 (Apr. 15, 1992), 57 Fed. Reg. 58942, 58946 (Dec. 11, 1992); See also 21 C.F.R. §§ 312.34, 312.81 (2007), and FDA, *Guidance for Industry: Fast Track Drug Development Programs—Designation, Development, and Application Review* (Rockville, Md.: Jan. 2006).

[43]In support of its arguments about the intent of the regulations, the sponsor cited the pertinent language from preambles to the proposed and final rules. See footnote 42.

restrictions requested by FDA. However, in a September 2000 letter to FDA, the sponsor agreed to FDA's requirement that approval be under Subpart H, while noting that it still believed that applying these regulations to Mifeprex was not appropriate.

- Conditions of Use: FDA reviewed data and held multiple meetings with the sponsor regarding the specific conditions of use that should be required for Mifeprex. For example, FDA deliberated about whether it was necessary to require that prescribing physicians possess the ability to perform follow-up surgical interventions in the event that it was necessary to manage complications. The sponsor maintained that such a requirement was inconsistent with the practice of medicine, because management of incomplete miscarriages was routinely handled by referring patients to outside providers with specialized surgical or emergency care training. On this issue, FDA concluded that access to follow-up care could be ensured by requiring adequate information in the labeling and requiring that physicians attest to having made arrangements for their patients to have access to any needed surgical or emergency care. The SGE consultant agreed with FDA's conclusion. FDA disagreed with the sponsor on other suggested conditions of use. For example, the sponsor provided data to support allowing patients to self-administer the misoprostol dose at home, instead of requiring them to return to their prescribing physicians. FDA concluded that the available data did not support the safety of home use of misoprostol and that such use should not be included in the final product label. As a part of its deliberations about the conditions of use, FDA also concluded that approved labeling should include a medication guide to provide patients with information about the risks and benefits of the drug and the approved conditions of use and treatment regimen.[44]

- Postmarketing Study Commitments: In both the September 1996 and February 2000 approvable letters, FDA had reminded the sponsor of its commitment to conduct a series of six postmarket studies to address comments raised in the 1996 advisory committee meeting. FDA reviewed data and met with the sponsor during the final stages of its review to revisit these commitments in light of experience gained with the treatment regimen since the advisory committee meeting, concerns about potential infringement on the privacy of patients, and the potential resources needed to fulfill all six commitments. FDA concluded that the originally proposed commitments could be sufficiently addressed in two redesigned

[44]FDA may require that a drug be distributed with a medication guide that provides patients with information about the safe and effective use of the drug. See 21 C.F.R. pt. 208 (2007).

studies. The first was a study on the safety outcomes of a group of patients receiving the treatment under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention when necessary. The second was a surveillance study to determine the outcomes of ongoing pregnancies that were not surgically terminated after a failure of the Mifeprex regimen, including the health of any children born. FDA also concluded that the outstanding questions could be incorporated into the two postmarket studies and an audit of signed patient agreement forms.

Once the sponsor had addressed the issues that FDA raised during the third review cycle, both the review team responsible for the Mifeprex NDA and FDA management concluded that the drug should be approved. The medical officer concluded that the updated safety data did not reveal any new issues that would change the ratio of benefit-to-risk for the drug. The medical officer also reviewed revised product labeling related to the distribution of the drug. Based on these reviews, the medical officer recommended approval of the application. The non-clinical reviews during this review cycle included additional inspections of manufacturing facilities. After the sponsor had addressed several issues, including deficiencies identified in a second inspection of the drug manufacturing facilities, the non-clinical reviewers also recommended approval of the application. FDA management concurred with the recommendations of the review team that the Mifeprex NDA should be approved.

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of Subpart H. The sponsor began distribution of Mifeprex in November 2000. FDA approved the drug with the two postmarketing study commitments discussed above and with several key restrictions on distribution. First, prescribing physicians must sign a prescriber's agreement attesting to possessing the training and skills needed to administer the treatment regimen, and also agreeing to provide patients with the approved medication guide. They must also attest that they will fully discuss the treatment with patients and report to the sponsor any serious adverse events or ongoing pregnancies that are not terminated after a failure of the Mifeprex regimen. Second, the drug must be distributed directly to prescribing physicians by an authorized distributor only after the distributor has verified that the physician has a signed agreement on file. Third, patients must sign a patient agreement attesting to having read, discussed, and understood the risks and potential complications of the treatment. For a more detailed list of the individual components of the restricted distribution program for Mifeprex, see

appendix II. For a copy of the approved prescriber's agreement, see appendix III.

Approval Process for Mifeprex Was Generally Consistent with That of the Other Eight Subpart H Restricted Drugs

Although each drug had unique risks and benefits, the approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs. Each of the drugs had unique risks and benefits that were specific to their indication and target populations. For some of the drugs, the safety issues that prompted FDA to apply Subpart H were similar, with the potential for causing birth defects, the potential for liver or other serious toxicities, and appropriate patient selection being the most common issues. However, there were also safe use concerns that were unique to particular drugs. For example, for Mifeprex, ensuring patient access to follow-up care was a key safety concern, while for Actiq a key concern was ensuring that children did not accidentally ingest the drug.[45] Each of the drugs represented potential advances in the treatment of their targeted condition and in two cases—Mifeprex and Xyrem—the drug was the first approved to treat that condition. (See app. I for a table including each of the Subpart H restricted drugs and their approved indications.)

One common element across the approval processes for the Subpart H restricted drugs was that for seven of the drugs, including Mifeprex, FDA needed to evaluate potential limitations in key clinical data supporting the NDA. Specifically, with the exception of Accutane and Lotronex, the drugs were approved on the basis of studies without concurrent controls or data that were limited by relatively small sample sizes or data collection issues.[46] FDA approved the Mifeprex NDA on the basis of historically controlled clinical trials that studied the drug in several thousand patients. FDA concluded that the use of historical controls was not a limitation

[45]Actiq contains the controlled substance fentanyl in a lozenge formulation intended to allow for more rapid delivery of the medication for pain management in patients who have developed a tolerance. Because of the formulation there are concerns that Actiq may be perceived by children as a lollipop.

[46]Both Accutane and Lotronex were approved under Subpart H after they had first been marketed in the United States. In the case of Lotronex, the sponsor withdrew the drug from the market in 2000 because of safety concerns. In 2002, FDA approved a supplemental NDA under Subpart H, allowing the drug to be marketed with a restricted distribution program and substantially more limited indication. For Accutane, which was originally approved for marketing in 1982, FDA approved a supplemental NDA under the restricted distribution provision of Subpart H in 2005 in order to require a more formal restricted distribution program that linked Accutane prescribing and dispensing to pregnancy testing results.

because the course of pregnancy was well-documented and the effect of the treatment was self-evident. Revlimid, Thalomid, Plenaxis, and Xyrem were also each approved on the basis of data that included at least one key clinical study that lacked a concurrent control.[47] In contrast to the Mifeprex data, FDA concluded that the lack of concurrent controls in these studies was a weakness because data on the course of the disease in a comparable population was not available to be used as a reliable historical control. For example, Thalomid was approved on the basis of clinical trial data from the published literature as well as a series of retrospective case studies for several dozen patients.[48] Additionally, five of the drugs—Actiq, Revlimid, Thalomid, Tracleer, and Xyrem—were approved on the basis of key clinical studies with relatively small sample sizes of several hundred patients or less. Finally, for Actiq, Plenaxis, Thalomid, and Xyrem, FDA identified data collection issues, such as incomplete documentation, in some of the key data sources.

Another common element was that for six of the drugs, including Mifeprex, FDA issued at least one prior action letter before ultimately approving the drug for marketing. FDA issued one approvable letter before ultimately approving Thalomid and Tracleer. Both Mifeprex and Xyrem received two approvable letters. In some cases the types of issues FDA cited—such as insufficient safety or efficacy data, the need for additional information on the restricted distribution system, or chemistry and manufacturing issues—were similar. For all four of these drugs, the adequacy of proposed distribution restrictions was a significant issue. For Xyrem, FDA's initial approvable action was also linked to the sufficiency of the data provided in the application. FDA issued not approvable letters for both Actiq and Plenaxis prior to their eventual approval. In the case of Actiq, FDA cited multiple deficiencies, such as reliance on a key clinical study with flaws and an inadequate plan for risk management. For Plenaxis, FDA initially concluded that the risks of the drug exceeded its

[47]FDA approved Plenaxis on the basis of one uncontrolled clinical trial in the indicated population—men with advanced symptomatic prostate cancer—and three concurrently-controlled clinical trials in men with less advanced prostate cancer. FDA approved Xyrem on the basis of one uncontrolled key safety trial, and two concurrently-controlled clinical trials.

[48]FDA considers such case studies to be historically controlled. In this case, the reviewing division concluded that the data were not sufficient to demonstrate the safety and efficacy of Thalomid. However, that decision was overridden by both the Director of the relevant FDA office and the Director of FDA's Center for Drug Evaluation and Research, based on their individual analyses of the available data.

benefits because of the potential for severe, systemic allergic reactions in patients.

As a result of these complexities, the approval process for the Subpart H restricted drugs was typically longer than the process for other drugs. Across the seven drugs with NDAs approved under Subpart H, an average of almost 25 months elapsed from the time that the sponsor submitted its NDA to the time FDA approved the NDA. The length of time to approval ranged from almost 9 months for Revlimid to more than 54 months for Mifeprex. In comparison, in analyses conducted for our 2006 report on new drug development, we found that it took FDA on average almost 18 months to approve NDAs submitted from 1996 through 2002.[49]

We also found that the types of distribution restrictions FDA imposed on Mifeprex were similar to those imposed on the other Subpart H restricted drugs, though the specifics of the restrictions depended on FDA's safe use concern for the drug.[50] (See table 2.) For all of the drugs except Actiq, FDA required some form of program enrollment or registration process. For example, for Mifeprex and three other drugs, FDA required that patients sign written agreements and that physicians enroll in a prescribing program and attest to their qualifications. For five of the drugs, FDA required formal registries of all prescribing physicians and patients.[51] Additionally, for seven of the drugs, FDA required that distribution be limited to authorized distributors or pharmacies.[52] And for eight of the

[49]See, GAO, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49. (Washington, D.C.: Nov. 17, 2006). In contrast, the drugs approved under the surrogate endpoint provision of Subpart H have generally been approved more rapidly than drugs approved under the restricted distribution provision of Subpart H and than drugs approved outside of Subpart H.

[50]Additionally, except for Plenaxis, FDA convened a meeting of the relevant advisory committee prior to each drug's approval under Subpart H to obtain expert input regarding the appropriate actions to address the agency's safe use concerns, including the distribution restrictions that should be required. The advisory committee meetings that FDA has held for the drugs Accutane and Lotronex occurred after each drug was first marketed in the United States, but prior to their approvals under Subpart H.

[51]FDA has used various types of registries as a mechanism to collect data on patients, providers, and others as a tool for monitoring outcomes of interest.

[52]Two of the drugs—Actiq and Xyrem—were approved as controlled substances and therefore subject to the restrictions imposed by the Controlled Substances Act. Requirements imposed under this act are enforced by the Drug Enforcement Administration and are distinct from the distribution restrictions imposed on these drugs by FDA under Subpart H. See, e.g., 21 U.S.C. § 822; 21 C.F.R. § 1301.11 (2007).

drugs, FDA required that the sponsor establish a process to ensure that dispensing or distribution of the drug was contingent on verification that physicians and others had enrolled or registered in the distribution program, or that patients had complied with certain safety measures. FDA also required that all of the sponsors implement some form of educational program for patients, prescribers, or pharmacists, though FDA did not require that prescribing physicians participate in formal training for any of the drugs. For six of the nine drugs, FDA required that the sponsor report periodically to the agency specifically on implementation of their restricted distribution programs. For seven of the drugs, FDA required that sponsors report to the agency on specific adverse events—such as fetal exposures or liver toxicity—more frequently than is required for other drugs. In the case of Mifeprex and Xyrem, at the time the drugs were approved, FDA did not require that the sponsors submit additional adverse event reports beyond those required for all approved drugs, but did require that physicians agree to report specific types of adverse events to the sponsor.

Table 2: Selected Features of Restricted Distribution Programs Imposed by FDA at Time of Approval under Subpart H

Features Required at Approval	Mifeprex (mifepristone)	Lotronex (alosetron hydrochloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Plenaxis (abarelix for injectable suspension)	Revlimid (lenalidomide)	Accutane (isotretinoin)
Program enrollment or registration[a]	✓	✓		✓	✓	✓	✓	✓	✓
Limited distribution channels[b]	✓			✓	✓	✓	✓	✓	✓
Dispensing or distribution contingent on verification[c]	✓	✓		✓	✓	✓	✓	✓	✓
Sponsor developed educational programs[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reporting specific to implementation of restricted distribution program		✓	✓	✓	✓		✓		✓
Additional adverse event reporting by the sponsor[e]		✓	✓	✓	✓		✓	✓	✓

Source: GAO analysis of FDA data.

[a]Program enrollment or registration requirements varied across the drugs. For Accutane, Lotronex, Mifeprex, and Plenaxis, FDA required that physicians enroll in a prescribing program and attest to their qualifications. For Accutane, Revlimid, Thalomid, Tracleer, and Xyrem, FDA required formal registries of all prescribing physicians and patients. FDA also required registration of pharmacies, wholesalers, or distributors for Thalomid, Revlimid, and Accutane.

[b]The specific limitations imposed on distribution channels varied across the drugs, and in some cases more than one limitation was required. These limitations included, for example, requiring that a drug only be distributed directly to prescribing physicians, allowing only authorized distributors or wholesalers to ship a drug, and allowing only registered or centralized pharmacies to dispense a drug.

[c]The verification mechanisms varied across the drugs. For example, for Mifeprex, an authorized distributor must verify that a physician has a signed prescriber agreement on file before distributing the drug. For Lotronex, before dispensing and drug, pharmacists must verify that prescriptions include a sticker that is only available to physicians enrolled in the prescribing program. For Accutane, Revlimid, and Thalomid, a registered pharmacy is required to confirm prescription authorizations and that patients have complied with requirements to use one or more methods of contraception before dispensing the drug.

[d]In general, sponsors were required to develop educational materials (such as patient information videos) for patients, and make educational materials and training programs readily available to prescribing physicians, pharmacists, and other groups involved in the restricted distribution program. For some of the drugs, dispensing pharmacists were required to participate in formal training. At the time of Subpart H approval, FDA required medication guides for all of the drugs except Actiq, Plenaxis, and Thalomid.

[e]Sponsors for seven of the drugs were required to submit 15-day alert reports on specific adverse events. Sponsors of four of the drugs were required to provide updates more frequently than typically required for events related to FDA's safe use concern for the drug. For Mifeprex, as part of their prescriber agreement, physicians agreed to report ongoing pregnancies, hospitalizations, transfusions, and other serious events to the sponsor. For Xyrem, FDA required that physicians agree to collect and report to the sponsor information on specific adverse events and inappropriate use of the drug.

Finally, eight of the nine Subpart H restricted drugs were approved with two or more postmarketing study commitments.[53] Each of these had at least one commitment that involved developing a postmarket study to monitor adverse events or patient outcomes of interest for that drug. The number of study commitments FDA required ranged from 2 to 10, depending on the drug. Additionally, for most of the drugs, including Mifeprex, the study protocols for the various commitments had not been finalized at the time of approval.

[53]FDA's approval of Accutane under Subpart H through a supplemental NDA did not include any postmarket study commitments.

FDA's Postmarket Oversight of Mifeprex Has Been Consistent with the Agency's Oversight of the Other Subpart H Restricted Drugs

The actions FDA has taken to oversee Mifeprex have been consistent with the actions it has taken to oversee the other Subpart H restricted drugs. FDA has relied primarily on information submitted by the sponsors of all the Subpart H restricted drugs and inspections for three of the drugs to oversee compliance with restricted distribution requirements. FDA has also relied on updates submitted by these sponsors to oversee compliance with postmarketing study commitments and has found that most have unfulfilled commitments. To oversee compliance with adverse event reporting requirements, FDA has reviewed a variety of safety information including reports submitted by the sponsors of all nine of the drugs restricted under Subpart H and has conducted inspections to evaluate compliance with reporting of adverse events for eight of the drugs. As a result, for most of the drugs, FDA has identified deficiencies in compliance with adverse event reporting requirements. To oversee reported adverse events FDA has used similar methods—such as monitoring, investigating, and addressing safety concerns—for Mifeprex and the other eight Subpart H restricted drugs. As a result of its oversight of safety data, FDA has identified postmarket safety concerns for most of the drugs and has used a variety of methods to communicate safety information to health care providers and the public. (See table 3 for an overview of FDA's postmarket oversight of these drugs.)

Table 3: Selected Features of FDA's Oversight of Postmarket Safety for Drugs Approved under Subpart H, as of May 2008

Oversight Activities and Findings	Mifeprex (mife-pristone)	Lotronex (alosetron hydro-chloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Plenaxis (abarelix for injectable suspension)	Revlimid (lenali-domide)	Accutane (isotretinoin)
FDA has completed inspection(s) to oversee compliance with distribution restriction requirements[a]	✓				✓	✓			
FDA has classified at least one postmarketing study commitment as unfulfilled[b]	✓	✓	✓	✓	✓		✓	✓	n/a
FDA has conducted inspection(s) to oversee compliance with adverse event reporting requirements[c]	✓	✓	✓	✓	✓	✓	✓		✓
FDA has identified a postmarket safety concern leading to communication of new safety information to public or health care providers[d]	✓	✓	✓	✓	✓	✓		✓	✓

Source: GAO analysis of FDA data.

Note: FDA provided or confirmed data on these selected features of oversight through May 2008.

[a]In May 2008, FDA officials told us that they had conducted such inspections for three additional drugs. However, the reports from those inspections were not yet available. Inspections were in addition to report review.

[b]FDA classifies unfulfilled postmarketing study commitments as ongoing, pending, delayed, released, or terminated; FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarketing study commitments and has submitted the final report for the third and final commitment.

[c]Inspections were in addition to report review conducted for all of the drugs. In the case of Revlimid, FDA inspected Celgene—the sponsor of both Revlimid and Thalomid—before Revlimid was approved in December 2005.

[d]Communication of new safety information includes activities such as changing product labeling, issuing Public Health Advisories and Safety Alerts, and distributing letters to health care providers.

To Oversee Compliance with Distribution Restrictions, FDA Relied on Information Submitted by All Drug Sponsors and Its Own Inspections for Some of the Drugs, Including Mifeprex

For all nine of the drugs that have been approved under the restricted distribution provision of Subpart H, FDA has relied mainly on information submitted by sponsors in required reports to oversee the sponsors' compliance with distribution restrictions. For six of the drugs—not including Mifeprex—FDA relied on reports specific to the drugs' restricted distribution programs.[54] The type of information provided by the sponsors in these documents included data on the operation of the restricted distribution program, such as requirements for distributors, pharmacies, prescribers, and patients participating in the program. In addition, to oversee compliance with the restricted distribution programs for most of the drugs—including Mifeprex—FDA has relied on annual reports, supplemental applications, or periodic reports for required updates on the postmarket use of the drugs, including summaries of updates to the restricted distribution program.[55]

Through the end of 2007, FDA had conducted inspections specifically to oversee sponsors' compliance with distribution restrictions for three of the drugs—Mifeprex, Tracleer, and Xyrem. In the case of Mifeprex, in 2002 FDA conducted routine inspections of two of the drug's distributors to oversee their compliance with distribution restrictions. FDA inspectors reviewed standard operating procedures and other information in order to oversee adherence to the requirements of the restricted distribution program such as procedures for maintaining signed provider agreements, distributing medication guides with shipments of the drug, and maintaining the physical security of the drug. For one of the inspections of Mifeprex distributors, FDA did not issue a citation. For the other inspection, FDA issued a citation in which the agency cited four

[54]FDA approved six of the nine Subpart H restricted drugs with a requirement that the sponsor report periodically to FDA specifically on implementation of the respective restricted distribution program. Under FDAAA, sponsors of all drugs with an approved REMS will be required to submit periodically to FDA an assessment of their REMS. Pub. L. No. 110-85, § 901(b), 823 Stat. 929, 932, *codified at* 21 U.S.C. § 355-1.

[55]Though FDA's Subpart H regulations provide an expedited process for withdrawing marketing approval for a drug if FDA determines that promotional materials are false or misleading, the agency has not done so for a Subpart H drug. See 21 C.F.R. § 314.530(a)(5) (2007). However, it has issued warning letters citing the sponsors for two of the drugs—Thalomid and Tracleer—for promoting unapproved use of the drug in violation of FDA regulations.

inconsistencies between the approved distribution plan and the distributor's standard operating procedures. For example, FDA cited the distributor for the absence of certain written procedures pertaining to the distribution of the drug. The sponsor responded to this citation, noting that at the time of approval the distribution plan did not require that distributors prepare such written procedures. Other examples of the inconsistencies FDA noted were serial numbers that had not been properly recorded on a shipping label as required for tracking purposes and the requirement that a medication guide be provided with each dose of the drug was not reflected in the written procedures for processing orders. As a result of its 2006 inspection of the Tracleer restricted distribution program, FDA did not issue a formal citation, but provided recommendations to the sponsor. In its 2007 inspection of the Xyrem restricted distribution program, FDA did not identify any specific deficiencies.[56] However, many of the responsibilities for the program are contracted out to a pharmacy, which was not inspected. The inspection report notes that, for that reason, FDA could not verify whether the sponsor had fulfilled the requirements for the drug's restricted distribution program.

Although FDA's inspections for Mifeprex and Tracleer led to recommendations for improving the respective restricted distribution programs, through the end of 2007, FDA had not conducted inspections of compliance with restricted distribution requirements for six Subpart H restricted drugs. FDA officials told us that the agency has conducted

[56]FDA's inspection report notes that the sponsor refused to provide FDA access to full reports from audits that the sponsor had conducted to evaluate its contractors' compliance with agreed upon responsibilities under the restricted distribution program.

inspections of compliance with distribution restrictions for three additional drugs since the beginning of 2008.[57, 58]

To Oversee Compliance with Postmarketing Study Commitments, FDA Relied on Sponsors' Data That Found That Most Have Unfulfilled Commitments

For the eight Subpart H restricted drugs approved with postmarketing study commitments, FDA has relied on sponsors' annual reports for updates on the status of each commitment. FDA's reviews of these reports are the basis for its determination of the status of each commitment as fulfilled, submitted, pending, ongoing, delayed, released, or terminated. FDA officials told us that the status of postmarketing study commitments for Subpart H drugs is monitored the same way as those commitments for other drugs.

Seven of the eight Subpart H restricted drugs approved with postmarketing study commitments had at least one commitment that was not fulfilled as of September 2007.[59] Of these seven drugs, most have study commitments that FDA has classified as ongoing, pending, or delayed.[60] In the case of Mifeprex, FDA had categorized both of the drug's postmarketing study commitments—to which the sponsor agreed at time of the drug's approval in 2000—as ongoing until December 2007 when the agency changed the status of one of the commitments to released. For the first commitment—a study to compare outcomes for patients whose

[57]In 2008, FDA conducted initial inspections specific to the restricted distribution programs for Accutane, Actiq, and Revlimid. In addition, FDA conducted a second such inspection for the Tracleer program. As of May 13, 2008, the results from these inspections were not available.

[58]In February 2007, agency officials told us that they were working to establish a process to conduct regular inspections to oversee sponsors' compliance with distribution restrictions for Subpart H restricted drugs. Since that time, agency officials told us that FDA had decided to combine the inspection of restricted distribution programs with inspections examining compliance with adverse event reporting requirements. However, agency officials noted in May 2008 that FDA is reevaluating its process for conducting inspections in light of recent legislative changes. Under FDAAA, FDA is required to evaluate, at least annually, for one or more drugs that have elements to assure safe use as part of their REMS, whether those elements assure the safe use of the drug, are not unduly burdensome on patient access, and to the extent practicable minimize the burden on the health care delivery system. 21 U.S.C. § 355-1(f)(5)(B).

[59]FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarket study commitments and has submitted the final report for the third and final commitment.

[60]In its June 2006 report on FDA's management of postmarket studies, the Department of Health and Human Services Office of the Inspector General found that it is common across all drugs approved by FDA with postmarket study commitments for sponsors to have unfulfilled commitments.

health care providers perform a surgical abortion with outcomes for patients who are referred to another facility for follow-up care in the event of treatment failure—the sponsor has reported difficulty in enrolling participants into the study. FDA told us that according to the sponsor, the "vast majority of prescribers" can provide surgical abortion services on site. FDA has opted not to terminate the study, and has categorized it as ongoing. FDA officials told us that this gives the agency additional flexibility in the event that provider or practice patterns change over time, making enrollment of study participants more feasible. The sponsor also has reported enrollment challenges in the case of the second study commitment for Mifeprex—to conduct surveillance of ongoing pregnancies following failure of treatment. FDA officials told us that postmarket experience with the drug has shown that most patients opt to have a surgical abortion in the event that the Mifeprex regimen is not successful in terminating the pregnancy. In December 2007, FDA released the sponsor from this commitment because it determined that the study will no longer provide helpful information because of low enrollment.

FDA has worked with some of the sponsors of the Subpart H restricted drugs to make adjustments to agreed upon commitments that have not been completed.[61] FDA officials told us that the agency has in some cases made changes to a sponsor's postmarketing study commitments or requested new commitments in addition to those specified at approval. For example, FDA recommended several additional postmarketing study commitments for Thalomid following the agency's approval of an expanded indication for the drug. In the case of Tracleer, FDA recommended changes to some of the drug's study commitments. FDA had not requested additions or changes to the postmarketing study commitments for Mifeprex until the agency released the sponsor from its commitment to conduct surveillance of ongoing pregnancies following failure of treatment.

[61]FDA may withdraw approval of a drug approved under Subpart H if a sponsor does not carry out its required postmarketing studies with due diligence. 21 C.F.R. § 314.530(a)(2) (2007). According to FDA, the regulations only require postmarketing study commitments for drugs approved under the surrogate endpoint provision (21 C.F.R. § 314.510) and not for drugs approved under the restricted distribution provision (21 C.F.R. § 314.520). FDAAA provides FDA with additional authority with regard to requiring postmarketing studies and/or trials. See 21 U.S.C. § 355(o)(3).

To Oversee Compliance with Adverse Event Reporting Requirements, FDA Reviewed Sponsors' Data, Conducted Inspections and Identified Deficiencies for Most of the Drugs

To oversee compliance with adverse event reporting requirements, FDA has both reviewed data submitted by sponsors in required reports and conducted inspections. Sponsor reporting for the drugs has included annual reports in which the sponsor provided a summary of the adverse events reported in the previous year; periodic update reports which inform FDA of adverse events monthly, quarterly, or at some other interval established by FDA; and 15-day alert reports for events that are both serious and unexpected. In addition, in some cases sponsors have agreed or FDA has required them to provide 15-day alert reports for other types of serious adverse events. For example, the sponsor of Mifeprex agreed to provide 15-day alert reports for cases of serious infection and ruptured ectopic pregnancy in women who used the drug, and FDA required the sponsor of Thalomid to report suspected or confirmed pregnancy in women taking that drug.[62] In some cases, including for Mifeprex, FDA specifically documented its assessments of adverse event reporting contained in annual, periodic update, or 15-day alert reports or reports submitted to the AERS database. FDA officials told us that staff review all submitted reports, but do not always document their reviews.

In addition to relying on reports submitted by the sponsors, FDA has conducted inspections specifically to oversee the sponsors' compliance with adverse event reporting requirements for eight of the nine drugs, including Mifeprex.[63] Between 2001 and May 2008, FDA had conducted 19 such inspections with a range of none to four inspections conducted for each drug.[64] In the case of Mifeprex, FDA has conducted three inspections—in 2002, 2004, and 2006—related to adverse event reporting. In these inspections, FDA reviewed a variety of documents pertaining to adverse event reporting for Mifeprex, including standard operating procedures, product labeling, MedWatch reporting forms, 15-day alert

[62]Mifeprex labeling specifically cautions against the use of the drug in women with ectopic pregnancy. The sponsor has noted that the condition is not an adverse drug experience as FDA defines the term.

[63]As of May 2008 FDA had not conducted an adverse event reporting inspection for the sponsor of Revlimid since this drug was approved under Subpart H. The agency inspected Celgene—the sponsor of Revlimid and Thalomid—in 2001, 2002, 2004, and 2005, but these inspections occurred before Revlimid was approved in December 2005. FDA officials told us they did not have specific goals for how frequently sponsors are inspected to monitor compliance with adverse event reporting requirements.

[64]These inspections include two inspections of the sponsor of Accutane (isotretinoin). FDA conducted an additional four adverse event reporting inspections of sponsors or the manufacturer of generic isotretinoin products.

reports, complaint file, periodic update reports on adverse events, and annual NDA reports. In addition, FDA documented reviews of samples of the sponsor's adverse event reports for completeness, accuracy, and timeliness.

As a result of the Mifeprex inspections, FDA issued citations for deficiencies related to the accuracy, completeness, or timeliness of some reports as well as for the sponsor's failure to follow certain procedures for handling some adverse event follow-up activities. In each of the Mifeprex inspections, FDA identified some examples of misclassified reports—events which FDA said should have been submitted as 15-day alert reports rather than in periodic reports. For example, FDA cited the sponsor for not classifying some events resulting in hospitalization as serious events and thus not reporting those events as 15-day alert reports. In another inspection, FDA found that some of the sponsor's procedures for reporting and following up on adverse events were inadequate or had not been developed. These deficiencies were similar to those FDA found for other drugs, and FDA identified fewer problematic reports for Mifeprex than for some of the other Subpart H restricted drugs. Following each of the inspections for Mifeprex, the sponsor provided a written response to FDA in which it either agreed to address FDA's findings or noted its disagreement with the deficiencies FDA cited. For example, following the first inspection, the sponsor agreed to address the examples of misclassified or incomplete reporting FDA cited and to reinforce procedures for handling adverse event-related correspondence with its staff. In some cases the sponsor disagreed with FDA's characterization of a deficiency or presented evidence to refute a claim that it had not complied with a reporting requirement or procedure.

As a result of FDA's inspections for the other seven drugs, the agency issued written citations to six of the sponsors for deficiencies. In addition, FDA noted only "oral observations" for the other sponsor. Similar to the Mifeprex inspections, FDA staff reviewed information such as sponsor documentation and standard operating procedures related to adverse event reporting for the other seven drugs for which it conducted inspections. As it did for the Mifeprex inspections, FDA reviewed samples of adverse event reports for completeness, accuracy, or timeliness for most of the other drugs. As it did with Mifeprex, FDA cited some sponsors for deficiencies such as incomplete or late reporting of adverse events or failure to adhere to certain procedures for reporting. For example, FDA cited the sponsor of Thalomid for failure to submit several reports of serious and unexpected adverse events as a 15-day alert report and for late reporting of some other adverse events that included deaths and

hospitalizations. In addition, FDA issued an untitled letter to the sponsor citing its failure to review and submit 82 reports of serious and unexpected adverse events within the required time frame.

FDA was not always consistent in how it documented deficiencies in adverse event reporting. In some of its inspections FDA documented the same type of deficiency as a citation while in others it noted them as oral observations or discussion points. For example, FDA did not issue a citation for the sponsor of Tracleer after inspectors noted 52 late 15-day reports—instead discussing the late reports with the sponsor at the close of the inspection. However, in its first inspection of the sponsor for Mifeprex, FDA issued a citation for failure to file a single 15-day report within the required 15 days. FDA also cited the sponsor for 6 late 15-day reports in each of its two subsequent inspections, although the sponsor refuted this finding in written responses following each inspection. As in the case of Mifeprex, sponsors responded to FDA in writing to describe actions they had taken to address deficiencies or to disagree with FDA's conclusions following an inspection.

To Oversee Postmarket Safety, FDA Used Similar Methods to Review Reported Adverse Events and Took a Variety of Actions in Response to Emerging Concerns

FDA has used similar methods to oversee postmarket safety—monitoring, investigating, and taking action on emerging safety concerns—for Mifeprex and the other eight Subpart H restricted drugs. For Mifeprex, FDA has routinely reviewed the available information on reported adverse events from sources such as annual reports, periodic update reports, 15-day alerts, and data from its AERS database. Since the time Mifeprex was approved, FDA has documented regular reviews and summarized the available data on adverse event reports to monitor the drug's safety. FDA believes that, because the distribution system for Mifeprex requires that prescribing physicians agree to report hospitalizations and other serious adverse events, it is unlikely there are significant numbers of these events that are not reported to FDA. However, FDA acknowledges that because the reporting system is voluntary, the agency cannot be certain that they have reports of all serious adverse events.

FDA officials have concluded that, with the exception of the cases of fatal infection, the reported serious adverse events associated with Mifeprex have been within or below the ranges expected based upon the medical literature on adverse events following medical abortion. In its May 2006

response to congressional inquiries regarding Mifeprex,[65] FDA stated that the most commonly reported serious adverse events had been blood loss requiring a transfusion, infection, and ectopic pregnancy. FDA estimated that 0.023 percent of U.S. women who had taken Mifeprex have required transfusion, compared to a transfusion rate of 0.15 percent observed in international studies of the drug. FDA also noted that the rate of ectopic pregnancy among U.S. women who had used Mifeprex was 0.005 percent, compared to the overall rate of 1.3 to 2 percent in all U.S. pregnancies. Based on the medical literature, FDA estimated that fewer than 1 percent of patients will develop an infection of any kind following medical abortion with Mifeprex.

According to FDA, as of May 2008, among the estimated 915,000 U.S. women who had taken Mifeprex for termination of pregnancy since its approval, the agency was aware of seven deaths that may be related to the use of the drug.[66] Six of the deaths were due to severe infection, and one death involved an undiagnosed ectopic pregnancy. Of the cases involving infection, five of the women were infected with a rare bacterium, *Clostridium sordellii*, while one woman was infected with the bacterium *Clostridium perfringens*. With assistance from the Centers for Disease Control and Prevention (CDC) and other outside experts, FDA has investigated all reported infection-related deaths in U.S. women who have taken the Mifeprex regimen for termination of pregnancy. These investigations included requesting the medical records and autopsy reports for each case; evaluating available adverse event data from the United States, the United Kingdom, and the World Health Organization; consulting with scientific experts and health care providers from inside and outside FDA; and microbiological testing to identify the bacterium involved. In addition, FDA evaluated samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths to test for contamination with the bacteria.[67] FDA found that in the six cases of death

[65]FDA statement to the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, May 17, 2006.

[66]In her testimony to Congress on May 17, 2006, Dr. Janet Woodcock stated FDA was aware of five infection-related deaths in U.S. women. In the course of GAO's research for this study, FDA reported that an additional infection-related death occurred in 2007. In her testimony, Dr. Woodcock also discussed three other cases of deaths in U.S. women who had taken Mifeprex that, following investigation, were determined unlikely to be related to the use of the drug. In addition, she discussed three women in other countries whose deaths were related to the use of mifepristone and misoprostol for medical abortion.

[67]The product tracking provision of the restricted distribution program for Mifeprex enabled FDA to locate the lot numbers for the drugs administered in each of the cases.

due to infection, the women used a regimen of Mifeprex and misoprostol that has not been approved by FDA.[68] FDA has stated that it is aware that many health care providers use modified regimens, and while some of the regimens have been described in the medical literature, FDA has not evaluated the safety and effectiveness of any other regimen than the one described in the drug's approved labeling.

To further explore the nature of the infections, FDA initiated an interagency scientific workshop in May 2006 with CDC and the National Institutes of Health entitled "Emerging Clostridial Disease." These agencies had observed a general increase in the United States in reports of serious clostridial infections including infections in women who had used Mifeprex, that raised questions about *Clostridium's* relationship to fatal illness and pregnancy. According to the meeting minutes, participants discussed recent cases of clostridial infection—including those occurring among women who had taken Mifeprex and misoprostol for termination of pregnancy and those who had not—reviewed what was currently known about these infections, and discussed how to conduct surveillance to ensure that cases and trends of clostridial infections are monitored. At the workshop, a CDC official reported on the history of clostridial infections, including a cluster of ten fatal cases reported in the literature between 1977 and 2001 among previously healthy women. Of the ten cases, eight of the women became infected following childbirth, one became infected following a medical abortion, and the other case was unrelated to pregnancy.

As a result of its investigative efforts, FDA has concluded that the evidence does not indicate that Mifeprex caused the fatal infections. In response to congressional inquiry, FDA stated that "the nature of the relationship between taking a single dose of the drug and the reported cases of serious infection with a rare bacterium is highly uncertain."[69] Laboratory testing of samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths due to infection has

[68]In the case of five of the deaths in the U.S. due to infection, the women used an oral dose of Mifeprex, followed by a dose of misoprostol taken intravaginally. In the other case of death due to infection, the woman used an oral dose of Mifeprex followed by a dose of misoprostol taken by inserting it in the pouch of the cheek. The regimen approved by FDA calls for swallowing doses of both Mifeprex and misoprostol.

[69]See FDA letter to Representative Mark E. Souder, then-Chairman of the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, U.S. House of Representatives, July 31, 2006.

shown no evidence of contamination with the bacteria.[70] FDA officials have said that the relationship between the infections and the use of unapproved regimens of Mifeprex and misoprostol remains unknown. Some research has suggested that the use of Mifeprex may suppress the immune system which could lead to infection. However, FDA has noted that if this were the case, the agency would expect to see a higher rate of other types of serious infections in patients who had used the drug, which has not been the case. FDA has noted that findings by the CDC and in the medical literature suggest that pregnancy itself—rather than the medication—may be the critical risk factor for women who have become infected with *Clostridium sordellii*.

FDA, working with the drug's sponsor, has taken a variety of steps—such as issuing warnings and making changes to the product labeling—to address safety concerns for Mifeprex that were identified through postmarket monitoring and investigation. For example, in response to reports of ruptured ectopic pregnancy, FDA developed a questions and answers document about the condition and worked with the drug's sponsor to alert health care providers and to highlight the importance of careful screening for the condition. In addition, FDA approved a labeling change to provide information about the importance of evaluating patients for ectopic pregnancy. In response to concerns about serious infections and associated deaths—all of which involved an off-label use of the drug—FDA issued Public Health Advisories to notify healthcare providers about patient deaths and the treatment regimens used in those cases, and to remind them of the regimen FDA has approved, and that FDA has not established the safety of alternative regimens. In addition, FDA issued a news release, reviewed letters from the sponsor to health care providers and emergency room directors to alert them to the safety concerns regarding serious infection, and approved changes to product labeling including revisions to the warning to include information about the deaths due to serious infection.[71] FDA also has established a Web site with information about Mifeprex, questions and answers about the drug, and

[70]FDA officials told us that the agency did not test for bacterial contamination of the specific lot associated with the most recent death because examination of the prior lots revealed no contamination.

[71]FDA officials told us that the sponsor distributed a letter to all health care providers who had signed the prescriber's agreement as of the time of the distribution of the letter and distributed a letter to all emergency room directors in the United States.

links to other safety-related information.[72] FDA used labeling changes—including updating the medication guide that prescribers agree to discuss with their patients—and information posted on its Web site to remind consumers and health care providers that FDA has not assessed the safety and efficacy of any regimen other than the one approved for the drug and indicated in its labeling.

FDA has similarly monitored adverse events for the other Subpart H restricted drugs. As FDA has done with Mifeprex, the agency has documented periodic safety reviews of the available information it had on reported adverse events for all of the other drugs. FDA's reviews analyzed data on reported adverse events from sources such as annual NDA reporting, periodic update reports, 15-day alerts, and data from the AERS database. Some FDA reviews summarized the available data on a specific type of adverse event—like liver toxicity, or severe bleeding—or adverse events in general, in order to determine whether the data suggest an emerging safety concern for the drug. In addition, in some cases, as it did with Mifeprex, FDA has sought the advice and assistance of other federal agencies and outside experts to investigate serious adverse events.

As a result of its monitoring activities, FDA has identified postmarket safety concerns for most of the Subpart H restricted drugs and has taken similar actions to address them. When FDA has found safety concerns related to a Subpart H restricted drug, it has worked with the drug's sponsor to employ a variety of measures to ensure the drug's safe use. These have included adding or strengthening a warning on the label, issuing a Public Health Advisory, and sending letters to health care providers to alert them to a safety risk. FDA has approved safety-related labeling changes, such as boxed warnings, for eight of the nine drugs. In the case of four of the drugs, including Mifeprex, the agency issued a Public Health Advisory or Safety Alert. The sponsors of five of the drugs including Mifeprex sent a letter to health care providers who prescribe (or may prescribe) the drug to alert them of safety concerns or to communicate new information regarding the drug. For example, in the case of Tracleer, adverse event reports revealed an increased risk of liver damage in patients who were treated with the drug. As a result, FDA and the sponsor notified health care providers of the risk by issuing a Safety Alert, highlighting the need for continued monitoring of liver function in

[72]FDA's Web site for Mifeprex safety information is located at: http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm

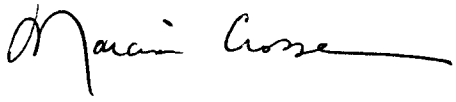
patients using the drug. The sponsor added a boxed warning about potential liver injury to the labeling and issued a letter to health care providers to alert them to the potential risk. In general, the actions FDA took in response to safety concerns were similar across all of the drugs.

Agency Comments

We provided HHS with a draft of this report for review. HHS informed us that it did not have general comments on the draft report. In addition, HHS provided technical comments, which we incorporated as appropriate.

As we agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of this letter. We will then send copies to others who are interested and make copies available to others who request them. In addition, the report will be available at no charge on GAO's Web site at http://www.gao.gov.

If you or your staffs have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.



Marcia Crosse
Director, Health Care

Appendix I: Select Drugs Approved by FDA with Restricted Distribution

Drugs approved under the restricted distribution provision of Subpart H	Condition treated	Application type (year first approved under Subpart H)
Accutane (isotretinoin)	Severe recalcitrant nodular acne.	Supplemental NDA (2005)
Actiq (oral transmucosal fentanyl citrate)	Management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy.	NDA (1998)
Lotronex (alosetron hydrochloride)	Severe diarrhea predominant irritable bowel syndrome (IBS) in women who have: chronic IBS symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and failed to respond to conventional therapy.	Supplemental NDA (2002)
Mifeprex (mifepristone)	Medical termination of intrauterine pregnancy through 49 days' pregnancy.	NDA (2000)
Plenaxis (abarelix for injectable suspension)	Palliative treatment of men with advanced symptomatic prostate cancer, with specified risks or symptoms.	NDA (2003)
Revlimid (lenalidomide)	Treatment of a limited subset of patients with transfusion dependent anemia.	NDA (2005)
	Treatment of multiple myeloma patients who have received at least one prior therapy.	Supplemental NDA
Thalomid (thalidomide)	Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrences.	NDA (1998)
	Newly diagnosed multiple myeloma.	Two Supplemental NDAs[a]
Tracleer (bosentan)	Pulmonary arterial hypertension.	NDA (2001)
Xyrem (sodium oxybate)	Cataplexy associated with narcolepsy.	NDA (2002)
Select Drugs with restricted distribution imposed outside of Subpart H		**Application type (year first approved)**
Clozaril (clozapine)	Management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.	NDA (1989)
Tikosyn (dofetilide)	Irregular heartbeats (atrial fibrillation and atrial flutter).	NDA (1999)
Trovan (trovafloxacin/ alatrofloxacin)	Serious, life- or limb-threatening infections in an inpatient healthcare setting.	n/a[b] (1997)

Source: GAO analysis of FDA data.

Note: We list each drug by its trade name with its chemical name in parentheses.

[a]These supplemental NDAs were approved under both the restricted distribution and surrogate endpoint provisions of Subpart H.

[b]Trovan was not originally approved with distribution restrictions. Based on postmarket evidence of serious liver injury in some patients, the sponsor agreed to FDA's requests to limit the distribution of Trovan to patients with specific symptoms only in inpatient settings. However, these restrictions were not associated with a supplemental application.

Appendix II: Detailed Description of Distribution Restrictions for Mifeprex

FDA approved Mifeprex with the following specific restrictions on distribution:

- Mifeprex must be provided by or under the supervision of a physician who possesses adequate qualifications and agrees to provide the treatment according to several guidelines. To accomplish this, the system required that prescribing physicians register with an authorized distributor by providing a signed Prescriber's Agreement attesting to the following:
  - Possesses the ability to assess the duration of pregnancy accurately.
  - Possesses the ability to diagnose ectopic pregnancies.
  - Possesses the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or has made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
  - Has read and understood the prescribing information about Mifeprex.
  - Will provide each patient with a medication guide and fully explain the procedure to each patient, provide her with a copy of the medication guide and Patient Agreement, give her an opportunity to read and discuss both the medication guide and the Patient Agreement, obtain her signature on the Patient Agreement and sign it as well.
  - Will notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
  - Will report any hospitalization, transfusion or other serious events to the sponsor or its designate.
  - Will record the Mifeprex package serial number in each patient's record.
- Provisions for the physical security of the drug during distribution such as
  - Direct distribution of the drug through select authorized distributors to physicians who have signed the Prescriber's Agreement, which includes providing their medical license number. Distributors are

required to ensure that the physician is registered before distributing the drug.

- Secure manufacturing, receiving, distribution, shipping, and return procedures, including unique serial numbers on packaging and tamper-proof seals.

Appendix III: Prescriber's Agreement for Mifeprex Distribution

The following is the prescriber's agreement at the time of the Mifeprex approval. Under the restricted distribution program for Mifeprex, the agreement is provided—by the sponsor's licensee Danco Laboratories, Inc.—to all providers to be signed and returned before the prescriber can receive any shipments of Mifeprex.

MIFEPREX™
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the

event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this serial number in each patient's record.

Danco Laboratories, LLC
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New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
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Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crossem@gao.gov.

Acknowledgments

In addition to the contact named above, Martin T. Gahart, Assistant Director; Jill Center; Chad Davenport; and Cathy Hamann made key contributions to this report. Julian Klazkin also contributed.

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United States Government Accountability Office

Report to Congressional Requesters

March 2018

FOOD AND DRUG ADMINISTRATION

Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts

GAO-18-292

March 2018

FOOD AND DRUG ADMINISTRATION

Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts

GAO Highlights

Highlights of GAO-18-292, a report to congressional requesters

Why GAO Did This Study

FDA initially approved Mifeprex in 2000 and restricted the drug's distribution to assure its safe use. In 2011, the agency approved a REMS for the drug. In March 2016, FDA approved an application for changes to the indication and dosing regimen for Mifeprex, which were reflected in revised labeling. Other changes included omitting the requirement that the prescriber be a physician. At that time, FDA also made modifications to the REMS. Some have questioned the safety implications of these changes for women using the drug.

GAO was asked to review FDA's relabeling of Mifeprex. GAO describes (1) the information FDA used to make its decisions regarding the relabeling of Mifeprex; and (2) what FDA's monitoring of Mifeprex has revealed, and stakeholders' views of FDA's monitoring and the safety of the drug.

GAO reviewed documents related to Mifeprex's relabeling, including FDA policies and regulations. GAO analyzed adverse event reports related to Mifeprex and reviewed FDA inspection reports of Mifeprex's sponsor. GAO also examined studies and data related to the safety and use of Mifeprex, and obtained information from FDA officials; Mifeprex's sponsor; and 13 stakeholder organizations, including medical associations and advocacy groups selected on the basis of their medical or scientific expertise, relevant publications, or familiarity with the drug's safety.

The Department of Health and Human Services provided technical comments on a draft of this report, which we incorporated as appropriate.

View GAO-18-292. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

The Food and Drug Administration (FDA) followed its standard review process when it approved the application and revised labeling reflecting certain changes, including the indication and dosing regimen, for the drug Mifeprex, which is used for the medical termination of early pregnancy. It based its approval on reviews of peer-reviewed published studies, articles, and other information submitted by Mifeprex's sponsor. These studies focused on topics related to the proposed labeling changes, including revision of the dosing regimen, increased gestational age, method of follow-up care, and type of health care provider authorized to prescribe Mifeprex. FDA also received three letters from advocacy groups requesting that FDA revise the Mifeprex labeling in a manner that would reflect clinical practice. In addition, FDA reviewed the Risk Evaluation and Mitigation Strategy (REMS)—a set of restrictions beyond the label that FDA may impose—associated with Mifeprex, and determined it continued to be necessary. FDA also reviewed adverse events—which the agency refers to as any untoward medical event associated with the use of a drug in humans, whether or not the event is considered to be drug related—associated with Mifeprex. It determined that the rates of certain adverse events remained stable and acceptably low. In addition, FDA reviewed information regarding potential risks of specific conditions associated with the use of Mifeprex and revised the labeling accordingly. FDA determined that the information it reviewed supported the changes to the Mifeprex labeling.

FDA has conducted a variety of monitoring activities and these have not identified significant concerns with the safety and use of Mifeprex, in accordance with its approved REMS.

- FDA has conducted three inspections of Mifeprex's sponsor since 2008 regarding adverse event reporting associated with Mifeprex—in 2010, 2014, and 2016—and identified minor deficiencies, such as the use of an outdated reporting form.
- FDA conducted a REMS compliance inspection in 2014 and did not identify any deficiencies.
- FDA identified approximately 4,200 instances of adverse events associated with Mifeprex from September 28, 2000, through June 30, 2017, among the approximately 3.2 million women who have used the drug. FDA identified 20 deaths in this period—a rate much lower than for women who proceeded to live birth. FDA learned of 2 additional deaths associated with Mifeprex since June 30, 2017.

GAO found that the views of stakeholder organizations were mixed regarding FDA's monitoring of Mifeprex. Positive comments included that the agency has a comprehensive monitoring program and a robust adverse event reporting system. Criticisms included that adverse events may be underreported and that FDA may only be aware of a fraction of them. Similarly, stakeholder organizations shared mixed views on the drug's safety. Positive comments included that the mortality rate associated with Mifeprex is extremely low. Safety concerns included that the revised labeling no longer requires patients to have a second visit with a health care provider, and that certain safety issues may be exacerbated by the increased gestational age limit approved by FDA.

United States Government Accountability Office

Contents

Abbreviations

FDA	Food and Drug Administration
FAERS	Food and Drug Administration Adverse Event Reporting System
HHS	Department of Health and Human Services
REMS	Risk Evaluation and Mitigation Strategy

U.S. GOVERNMENT ACCOUNTABILITY OFFICE
441 G St. N.W.
Washington, DC 20548

March 28, 2018

Congressional Requesters

The prescription drug Mifeprex, in combination with the prescription drug misoprostol, is used for the medical termination of early pregnancy. The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), initially granted marketing approval of Mifeprex in September 2000. As a condition of the drug's approval, FDA imposed restrictions on the distribution of Mifeprex under its general authority to help assure the safety and effectiveness of new drugs.[1] More than 3 million women in the United States are estimated to have used this drug.

We have previously reported on FDA's approval of Mifeprex and its oversight of the drug's safety, including the restrictions the agency placed on the drug's distribution.[2] Since that time, in 2011, FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex, with the goal of informing patients about the benefits and risks of Mifeprex, and to minimize the risk of serious complications associated with the drug.[3] In May 2015, Mifeprex's sponsor proposed several changes to the administration of the drug.[4] It submitted a supplemental new drug application to FDA to obtain approval to revise the drug's labeling.[5]

[1]See 21 C.F.R. § 314.520 (2000).

[2]GAO, *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex*, GAO-08-751, (Washington, D.C.: Aug. 7, 2008).

[3]A REMS is a set of restrictions specifically authorized by statute that FDA may impose to ensure that a drug's benefits outweigh its risks. See 21 U.S.C. § 355-1.

[4]A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable provisions of laws, such as the Federal Food, Drug, and Cosmetic Act and related regulations. Danco Laboratories, L.L.C., the sponsor of Mifeprex, is responsible for the marketing and manufacturing of Mifeprex, and submitted the supplemental application to FDA.

[5]Supplemental new drug applications are submitted to make certain changes to already approved new drug applications, including adding or modifying an indication or claim, or revising the dose or dosing regimen. FDA review and approval of most types of supplemental new drug applications is required before the drug may be marketed with these changes. FDA characterized the supplemental application submitted for Mifeprex as an efficacy supplement that, among other things, revised its dosing regimen. See 21 C.F.R. § 314.3 (2017). Throughout this report, references to the Mifeprex application pertain to this supplemental new drug application, submitted as an efficacy supplement.

Among other things, the sponsor proposed changing the dosing regimen, increasing the gestational age limit up to which Mifeprex can be taken, and eliminating the requirement that the dose of misoprostol be administered in a medical facility. FDA approved the labeling change in March 2016 and determined that the REMS continued to be necessary, with some modifications.

You and others have questioned whether the revised Mifeprex labeling has safety implications for the women who use the drug. For example, some stakeholder organizations, such as medical associations and research organizations, have raised concerns regarding FDA's postmarketing monitoring of Mifeprex and the drug's safety.[6] You asked us to report on FDA's relabeling of Mifeprex and its monitoring activities. This report describes

1. the information FDA used to make its decisions regarding the relabeling of Mifeprex; and
2. what FDA's monitoring of Mifeprex has revealed, and stakeholders' views of FDA's monitoring and the safety of the drug.

To describe the information FDA used to make its decisions regarding the relabeling of Mifeprex, we obtained information regarding the agency's review and subsequent approval of the revised Mifeprex labeling. Specifically, we reviewed documents in FDA's approval package for the Mifeprex supplemental new drug application. The approval package included FDA's assessments of the published literature submitted by Mifeprex's sponsor to support the safety and efficacy of the proposed changes.[7] Additionally, we reviewed other documents in the approval package, including communications between FDA and Mifeprex's sponsor during the application process, and the revised Mifeprex labeling and REMS. In addition, we studied FDA's assessments of adverse events associated with Mifeprex.[8] Finally, we examined federal regulations and FDA's policies and guidance documents, and interviewed FDA officials.

[6]The term postmarketing refers to activities occurring after a drug has been approved for marketing.

[7]FDA has posted documents pertaining to its review and approval on the agency's website (see https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm).

[8]FDA uses the term adverse event to refer to any untoward medical event associated with the use of a drug in humans, whether or not the event is considered to be drug related.

To describe how FDA monitors the safety and use of Mifeprex, we analyzed FDA's postmarketing adverse event summary reports associated with the use of Mifeprex from September 28, 2000, (when the drug was approved) through June 30, 2017, and obtained information from FDA officials regarding the agency's monitoring activities.[9] We also reviewed quarterly adverse event summary reports submitted to FDA by Mifeprex's sponsor for fiscal year 2017. To further describe FDA's monitoring, we reviewed documentation from inspections the agency conducted to determine the sponsor's compliance with relevant regulations and the Federal Food, Drug, and Cosmetic Act. Specifically, we reviewed FDA's reports from inspections of Mifeprex's sponsor for compliance with adverse event reporting requirements and the Mifeprex REMS that were performed since our 2008 report was issued.[10] We obtained information from FDA on the number and results of inspections that FDA has conducted since 2008 for compliance with current good manufacturing practices.[11] We also reviewed studies and data related to the safety and use of Mifeprex from FDA, stakeholders, and other entities. We discussed FDA's data collection processes and any limitations with agency officials and determined that the data we used were sufficiently reliable for the purposes of this report. We also obtained information from Mifeprex's sponsor on its perspectives of FDA's monitoring. Finally, to describe stakeholders' views of FDA's monitoring and the safety of the drug, we obtained information from 13 organizations, including medical associations and advocacy groups with a variety of perspectives for their

[9]FDA officials said that the adverse events associated with Mifeprex in its summary reports do not necessarily reflect a conclusion by the company or FDA that the drug caused or contributed to an adverse event. See 21 C.F.R. § 314.80(l) (2017).

[10]See GAO-08-751.

[11]Current good manufacturing practices provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210-21 (2017).

views on FDA's monitoring of Mifeprex, including any safety-related concerns they may have about the drug.[12]

We conducted this performance audit from April 2017 to March 2018 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

The treatment regimen of taking Mifeprex, in combination with misoprostol, works by both interrupting the hormones that the body needs to maintain a pregnancy and inducing the uterine cramping necessary to cause a medical abortion.[13] Mifepristone, the active ingredient in Mifeprex, was first approved in France and China in 1988, and is now approved in approximately 60 other countries, including the United States.

FDA's Review of New Drug Applications and Supplemental Applications

FDA must approve an application for a new drug before it can be marketed in the United States. FDA reviews scientific and clinical data contained in these applications as part of its process in considering them for approval to be marketed. FDA initially approved Mifeprex for use in the

[12]We obtained information from the following 13 organizations: the American Association of Pro-Life Obstetricians and Gynecologists; American College of Pediatricians; American Congress of Obstetricians and Gynecologists; Association of Reproductive Health Professionals; Bixby Center for Global Reproductive Health, University of California San Francisco; Charlotte Lozier Institute; Family Research Council; Guttmacher Institute; Gynuity Health Projects and the lead author of the Mifeprex REMS Study Group; Institute for Safe Medication Practices; National Right to Life Committee; Office of Population Research, Princeton University; and Planned Parenthood Federation of America. We selected these organizations on the basis of their medical or scientific expertise, their publication of relevant articles and web-based materials, or their familiarity with the safety and use of Mifeprex.

[13]Mifeprex is the trade name for one of the two mifepristone products approved and marketed in the United States (the trade name for the other product is Korlym, which has a different, unrelated indication). Mifepristone is the underlying drug substance and is also sometimes called RU-486, a reference to the name the drug had during laboratory testing. Medical abortion terminates a pregnancy using medications, rather than through a surgical procedure.

United States on September 28, 2000.[14] FDA approved the drug subject to restrictions that it considered necessary to ensure safe usage.

In addition to reviewing applications to market new drugs, FDA reviews supplemental new drug applications that drug sponsors submit to propose changes to an approved drug, such as adding or modifying an indication, revising the dose or dosing regimen, providing for a new route of administration, or changing the marketing status from prescription to over-the-counter use. As with original new drug applications, the agency assembles an internal team of reviewers—including medical officers, chemists, statisticians, pharmacologists, and other experts—to evaluate the information submitted in a supplemental application. During the review process, FDA may communicate with sponsors about issues that arise that may affect the approvability of the supplemental application. In response, sponsors can submit additional information to FDA in the form of amendments to the pending supplemental application. The review team compiles the results of its analyses and recommends to FDA management whether the supplemental application should be approved. Once the review is completed, the agency issues an action letter to the sponsor. FDA may approve the supplemental application (approval letter) or, if it determines it will not approve the supplemental application in its present form, it describes the specific deficiencies it identified in the supplemental application (complete response letter).

The review process for a drug application, including a supplemental application, may span several cycles before the agency approves the application.[15] For those applications that receive a complete response letter during a review cycle, the next FDA review cycle begins once the sponsor resubmits its application, providing responses to the deficiencies FDA identified in its previous review. These resubmissions often contain additional studies, analyses, data, or clarifying information to address FDA's concerns. The agency's review team examines the additional information provided by the sponsor, conducts any additional analyses

[14]In general, the mifepristone treatment regimens approved in other countries were similar to the regimen approved in the United States, although in some cases the specific drug used in combination with mifepristone was different than misoprostol.

[15]The first review cycle begins when FDA receives an application from a sponsor and ends when FDA issues an action letter. If FDA does not approve the application during the first review cycle, a new review cycle begins if the sponsor resubmits the application to provide responses to the deficiencies identified by FDA in the previous review cycle. See 21 CFR § 314.110(b)(1) (2017).

that are required, studies the results of any additional inspections that have been conducted, and again recommends either an approval or complete response action. As with the first review cycle, the process ends once FDA management reviews the recommendations of the review team and makes its decision on the action to take on the application.

Mifeprex's Supplemental Application

Prior to submitting its supplemental application, Mifeprex's sponsor met with FDA officials on January 29, 2015, to discuss the proposed labeling and Mifeprex REMS changes. At this meeting, both parties agreed that the sponsor should submit a supplemental new drug application covered by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.[16] On May 29, 2015, Mifeprex's sponsor submitted a supplemental application to FDA to revise the dosing regimen, amend the Mifeprex labeling, and modify the Mifeprex REMS. FDA's review for this supplemental application was classified as a standard review—as opposed to a priority review—with the performance goal of completing the application review and issuing an action letter to Mifeprex's sponsor within 10 months.[17] FDA approved the supplemental application on March 29, 2016, after one review cycle, meeting the agency's performance goal for the timely review of supplemental applications.[18] Table 1 shows key components of the original Mifeprex regimen and the revised regimen.

[16]This pertains to new drug applications that rely, at least in part, on investigations that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . ." See 21 U.S.C. § 355(b)(2). For example, such an application may rely on the finding of safety or effectiveness for an approved product or on published literature in addition to studies conducted by the sponsor.

[17]FDA generally grants priority review to applications for drugs that treat serious conditions and that, if approved, would provide significant improvements in safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies. FDA has a performance goal for completing priority reviews of supplemental applications in 6 months. FDA assigns a standard review designation to applications for drugs that do not meet the priority review designation criteria. FDA's goal is to generally complete review of these applications in 10 months.

[18]Food and Drug Administration, Mifeprex label, March 2016, accessed January 25, 2018, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

Table 1: Key Components of the Original Mifeprex Regimen and Prescriber Requirements, Approved in 2000, and the Revised Mifeprex Regimen and Prescriber Requirements, Approved in 2016

Regimen component	Original regimen	Revised regimen
Dosage	600 mg Mifeprex (mifepristone); 400 mcg misoprostol	200 mg Mifeprex (mifepristone); 800 mcg misoprostol
Dosing regimen	Day 1: 600 mg Mifeprex in a single oral dose. Day 3: 400 mcg misoprostol in a single oral dose if termination of pregnancy is not complete.	Day 1: 200 mg Mifeprex in a single oral dose. Day 2 or 3: 800 mcg misoprostol by buccal route (i.e., in the cheek pouch), 24 to 48 hours after taking Mifeprex.
Maximum gestational age (since first day of last menstrual period)	49 days	70 days
Prescriber requirements	To become certified, a licensed physician must sign and return the Prescriber Agreement Form to Mifeprex's sponsor.[a]	To become certified, a healthcare provider who prescribes must sign and return the Prescriber Agreement Form to Mifeprex's sponsor.[a]
Office visits and follow-up visits with prescriber, and location of dosing administration	Required three office visits by the patient: (1) 600 mg of Mifeprex administered to the patient by the physician or under the supervision of the physician in a clinic, medical office, or hospital. (2) Patient returns on day three for examination with physician; if termination of pregnancy is not complete, physician administers 400 mcg of misoprostol for patient to take orally. (3) Patient returns to physician for follow-up visit approximately 14 days after administration of Mifeprex to confirm complete termination of the pregnancy occurred.	Requires one office visit by the patient: (1) 200 mg of Mifeprex administered to the patient by the healthcare provider who prescribes, or under the supervision of a healthcare provider who prescribes, in a clinic, medical office, or hospital. (2) Patient takes 800 mcg of misoprostol by buccal route 24 to 48 hours after Mifeprex administration; the healthcare provider who prescribes discusses with the patient an appropriate location for her to be when she takes the misoprostol. (3) Patient should follow up with healthcare provider who prescribes approximately 7 to 14 days after Mifeprex administration to confirm complete termination of pregnancy has occurred and to evaluate the degree of bleeding.
Repeat misoprostol dose, if necessary	N/A	If the pregnancy has ended, but complete expulsion did not occur after the initial dose of misoprostol, the patient may be prescribed an additional 800 mcg of misoprostol to take buccally; women who choose to take a repeat dose of misoprostol should have a follow-up visit with their healthcare provider who prescribes in approximately 7 days to assess for complete expulsion.

Source: GAO analysis of information from the Food and Drug Administration. | GAO-18-292

[a]By signing the Prescriber Agreement Form, the prescriber certifies that he or she agrees with all specified requirements, including that the sponsor's Medication Guide will be supplied to all patients.

Mifeprex REMS

FDA initially approved a REMS for Mifeprex in June 2011.[19] When FDA approved the revised Mifeprex labeling in March 2016, the agency determined the REMS continued to be necessary, with some modifications.[20] Modifications from the original REMS to the revised REMS included

- changing the requirement that Mifeprex be provided "by or under the supervision of a physician" meeting specified qualifications to "by or under the supervision of a healthcare provider who prescribes" and meets such qualifications;
- changing the requirement for prescribers to agree to report to Mifeprex's sponsor any serious adverse event associated with Mifeprex, including hospitalizations and blood transfusions, to requiring prescribers to agree to report deaths associated with Mifeprex to the sponsor;[21]
- requiring Mifeprex's sponsor to report to FDA any death associated with Mifeprex, whether or not the death was considered drug-related, no later than 15 calendar days from the initial receipt of the information);[22] and
- removing the Medication Guide (which contained specific patient information, such as how to take Mifeprex and potential side effects) as an element of the REMS, although the Medication Guide remains part of the approved Mifeprex labeling, and the revised REMS requires the healthcare provider to provide a copy of the Medication Guide to the patient.[23]

[19]As part of a REMS, FDA can require "elements to assure safe use," 21 U.S.C. § 355-1(f)(1). This may include restrictions similar to those required to assure safe use under which Mifeprex was originally approved. 21 C.F.R. § 314.520 (2000).

[20]Food and Drug Administration, Mifeprex Risk Evaluation and Mitigation Strategy, March 2016, accessed January 25, 2018, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf.

[21]This requirement does not affect the sponsor's other reporting requirements under federal regulations.

[22]This requirement does not affect the sponsor's other reporting requirements under federal regulations.

[23]See 21 C.F.R. 208.24 (2017).

As part of the REMS, Mifeprex's sponsor is required to submit REMS assessments to FDA. The first REMS assessment was due one year from the date of initial approval of the REMS. Subsequent assessments are due every three years thereafter.[24] The REMS assessments include data on the cumulative number of health care providers enrolled in the Mifeprex REMS program; the number of providers ordering Mifeprex during the assessment reporting period; and the number of women exposed to Mifeprex, both cumulative and during the reporting period. In addition, they include copies of reports for certain adverse events, including hospitalizations due to complications, blood transfusions, serious infections, and deaths, as well as the cumulative numbers of these adverse events since the approval of Mifeprex and the number during the reporting period.

FDA's Postmarketing Oversight Activities

Federal regulations require sponsors of approved drugs to report periodically to FDA on safety information and specific types of adverse events that occur in association with their use.[25] Sponsors must provide in periodic reports—quarterly for the first three years after approval and annually thereafter—a narrative summary and analysis of adverse event information to FDA. For adverse events that are considered both serious and unexpected, sponsors are required to submit a Postmarketing 15-day Alert Report to FDA within 15 calendar days of initial receipt of the information.[26]

In some instances, FDA may request sponsors to study matters that it has determined worthy of further examination. Such requests are known as postmarketing study commitments and include studies or clinical trials that FDA has requested—and sponsors have agreed to conduct—to

[24]Mifeprex's sponsor submitted its first REMS assessment to FDA in June 2012, and the second one in June 2015.

[25]See 21 C.F. R. § 314.80 (2017).

[26]Serious adverse events are those that result in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of an existing hospitalization, a significant or persistent disability or incapacity, or a congenital anomaly or birth defect. Unexpected adverse events are those that are not included in the current labeling for a drug. Adverse events associated with a drug do not necessarily imply the drug caused the event.

address such issues.[27] FDA requires sponsors to report on the status of these studies in an annual report that also includes other information such as updates on the distribution of the drug, labeling changes, clinical literature published on the drug, and the drug's marketing.[28] FDA designates unfulfilled study commitments as submitted, pending, ongoing, delayed, released, or terminated.

FDA conducts postmarketing adverse drug experience inspections of sponsors to assess compliance with adverse event reporting requirements. FDA also conducts inspections of sponsors' compliance with the REMS, as applicable.[29] In addition, FDA inspects manufacturers for compliance with current good manufacturing practices. FDA classifies the results of each type of inspection in one of three ways:

- A classification of "official action indicated" means that objectionable conditions were found that may warrant regulatory action by the agency.
- A classification of "voluntary action indicated" means that objectionable conditions that do not meet the threshold for regulatory action were identified, and any corrective actions are left to the establishment to take voluntarily.
- A classification of "no action indicated" means that no objectionable conditions or practices were found during the inspection, or that the significance of the documented objectionable conditions found does not justify further FDA action.

To monitor and analyze adverse events associated with an approved drug, FDA compiles data from sponsors' reports on adverse events, as well as data from voluntary reports submitted to the MedWatch program, all of which are entered into FDA's Adverse Event Reporting System

[27]See Pub. L. No. 105-115, § 130, 111 Stat. 2296, 2331-2 (codified at 21 U.S.C. § 356b). Sponsors may also be required to conduct additional postmarketing studies or clinical trials (i.e., in connection with accelerated approval of drugs for serious conditions or approval based on animal efficacy data, or where determined necessary to identify or assess a serious risk related to use of a drug). See 21 U.S.C. §§ 355(o) (serious risk), 356(c)(2)(A) (accelerated approval); 21 C.F.R. § 314.610(b)(1) (2017) (animal efficacy data).

[28]See 21 C.F. R. § 314.81(b)(2) (2017).

[29]In 2008, we reported that FDA conducted three postmarketing adverse drug experience inspections of Mifeprex's sponsor in 2002, 2004, and 2006. The REMS for Mifeprex was not in place at that time. See GAO-08-751.

(FAERS).[30] FDA also established the Sentinel System, which may be used to monitor drugs using electronic health care data. This system complements FDA's existing monitoring capabilities, such as FAERS, by providing administrative and claims data that can be queried to monitor the use of FDA-regulated medical products and potential outcomes of treatment. The Sentinel System currently includes reimbursement data related to diagnoses, procedures, and drugs dispensed to over 223 million patients derived from 17 different data partnerships, including national health insurers and managed care organizations. While reimbursed health care encounters, procedures, and medications are included in the Sentinel System, those that are not reimbursable—such as visits to free health care clinics, drug samples given in physicians' offices, use of low-cost generic medications that do not incur an insurance copayment, or over-the-counter medications—generally are not captured.

FDA Reviewed Published Studies that Supported the Efficacy of the Proposed Mifeprex Labeling Changes, and Evaluated Safety Information and Adverse Event Data

In considering the supplemental application to revise the Mifeprex labeling, FDA reviewed 62 studies and articles that were submitted by the drug's sponsor related to different aspects of the efficacy and safety of the proposed changes. Over the course of FDA's application review, the agency also requested and received more detailed information from the authors of select publications through communication with Mifeprex's sponsor. Additionally, FDA evaluated adverse event data associated with Mifeprex.

[30]MedWatch is a voluntary reporting system through which health professionals and consumers can report adverse reactions, product problems, and errors in use related to drugs and other products approved by FDA.

FDA Reviewed Numerous Studies in Considering the Efficacy of the Proposed Changes to the Mifeprex Labeling

To determine the efficacy of the proposed changes to the Mifeprex labeling, FDA reviewed numerous published studies submitted by Mifeprex's sponsor, which included both U.S. and international studies.[31] Some of these studies assessed the efficacy of one component of the proposed Mifeprex labeling changes, such as the dosing regimen. Other studies assessed more than one component, such as home administration of misoprostol and the gestational age limit for Mifeprex. FDA also requested and received more detailed information from the authors of select publications through communication with Mifeprex's sponsor. In their review of the application, FDA reviewers identified what they considered major proposed changes. Some of the published studies submitted by Mifeprex's sponsor that FDA reviewed to support each of these proposed changes included the following:

- **Changes to the proposed dose and dosing regimen.** FDA reviewed 30 studies that evaluated changes to the dose and dosing regimen. For example, 22 of these studies, collectively, evaluated over 35,000 women who took the proposed dosing regimen—200 milligrams of Mifeprex orally and 800 micrograms of misoprostol buccally (i.e., in the cheek pouch) 24 to 48 hours after Mifeprex administration. The efficacy rates, defined as complete termination of the pregnancy without need for surgical intervention for any reason, ranged from 91 percent to 98 percent. One of these publications summarized the results of 20 studies, all but one of which used the proposed Mifeprex regimen in gestations through 70 days.[32] The overall efficacy rates in these 20 studies ranged from 97 percent to 98 percent for those studies that provided this information.
- **Extending the gestational age to 70 days.** FDA reviewed 19 studies that evaluated increasing the gestational age limit for taking Mifeprex. In addition to the publication discussed above that summarized the

[31]FDA accepts the use of peer-reviewed literature as primary or supportive data for an application under the framework of a 505(b)(2) application. See U.S.C. 21 § 355(b)(2). As part of its submission to FDA, Mifeprex's sponsor noted that it did not provide financial support or sponsor any of the studies submitted in its supplemental application. FDA's webpage pertaining to its review and approval of the Mifeprex supplemental application includes review documents (e.g., Cross Discipline Team Leader Review and Medical Review(s) documents) that contain lists and tables of references citing the publications FDA reviewed in the supplemental application (see https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm).

[32]M.J. Chen and M.D. Creinin, "Mifepristone with Buccal Misoprostol for Medical Abortion: A Systematic Review," *Obstetrics & Gynecology,* vol. 126, no.1 (2015): 12-21.

results of 20 studies, 4 of the studies that FDA reviewed evaluated the proposed dosing regimen through 70 days gestation.[33] Three of these studies evaluated the efficacy rates for gestational ages of 64 to 70 days, which ranged from 91 percent to 96 percent. The fourth study evaluated the efficacy rates through 70 days gestation when the drug was administered by physician providers (98 percent) and by nurse providers (98 percent). An additional publication submitted by the sponsor was a systematic review of studies that covered various dosing regimens, including the proposed regimen from 64 to 70 days gestation, which had a 93 percent efficacy rate.[34] Two other studies evaluated the efficacy rates from 64 to 70 days gestation, but used different dosing regimens than the proposed regimen, with efficacy rates of 92 percent for one study and 95 percent for the other study.[35] The remaining 11 studies evaluated efficacy rates for gestation greater than the then-approved 49 days gestation, but less than 64 days, with efficacy rates ranging from 87 percent to 100 percent.

- **Home administration of misoprostol.** FDA reviewed 15 studies that evaluated home administration of misoprostol, although FDA reported that none of these studies evaluated treatment outcomes with the use of misoprostol at home compared to a clinic setting. However, one study was a large literature review of 87 studies that included over

[33]The four studies were: (1) B. Winikoff, I.G. Dzuba, E. Chong, et al., "Extending Outpatient Medical Abortion Services through 70 Days of Gestational Age," *Obstetrics & Gynecology,* vol. 120 (2012): 1070-1076; (2) A.A. Boersma, B. Meyboom-de Jong, and G. Kleiverda, "Mifepristone Followed by Home Administration of Buccal Misoprostol for Medical Abortion up to 70 days of Amenorrhoea in a General Practice in Curacao," *The European Journal of Contraception & Reproductive Health Care,* vol. 16 (2011): 61-66; (3) P. Sanhueza Smith, M. Pena, I.G. Dzuba, et al., "Safety, Efficacy and Acceptability of Outpatient Mifepristone-Misoprostol Medical Abortion through 70 days Since Last Menstrual Period in Public Sector Facilities in Mexico City," *Reproductive Health Matters,* vol. 22 (2015): 75-82; and (4) C.D. Olavarrieta, B. Ganatra, A. Sorhaindo, T.S. Karver, A. Seuc, A. Villalobos, S.G. Garcia, M. Pérez, M. Bousieguez, and P. Sanhueza, "Nurse Versus Physician-Provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial," *Bulletin of the World Health Organization*, vol. 93 (2015): 249-258.

[34]D. Abbas, E. Chong, and E.G. Raymond, "Outpatient Medical Abortion is Safe and Effective through 70 Days Gestation," *Contraception,* vol. 92 (2015):197-199.

[35]The two studies were: (1) H. Bracken, R. Dabash, G. Tsertsvadze, et al., "A Two-Pill Sublingual Misoprostol Outpatient Regimen following Mifepristone for Medical Abortion through 70 Days' LMP: A Prospective Comparative Open-Label Trial," *Contraception*, vol. 89(3) (2014): 181-186; and (2) E.V. Gouk, et al., "Medical Termination of Pregnancy at 63-83 Days Gestation," *BJOG: An International Journal of Obstetrics and Gynaecology*, vol. 106 (1999): 535-539. FDA noted that these two studies were relevant because the dosage levels and routes of administration were expected to have similar or lower effectiveness than the proposed dosing regimen.

45,000 women evaluated using a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration, and dosing intervals in gestations through 63 days.[36] Half of the studies in this review did not require women to take misoprostol in a clinic. The results showed that the rates of treatment failure and ongoing pregnancy were very similar regardless of whether misoprostol was taken in a clinic or at another location. A further analysis of factors leading to increased failure found no evidence that home use of misoprostol increased rates of treatment failure or serious complications.

- **Use of a repeat misoprostol dose.** FDA reviewed 10 studies to support the use of a repeat dose of misoprostol. This repeat dose would be taken in instances when complete expulsion did not occur after the initial misoprostol dose and Mifeprex dose. For example, one study evaluated 68 women who did not have complete expulsion after taking Mifeprex and were given a second vaginal dose of misoprostol, with an efficacy rate of 62 percent.[37] In another study that evaluated the proposed regimen through 70 days gestation, 5 of 330 women took a second dose of misoprostol, because of the absence of bleeding after the first dose of misoprostol. The study found that one of the five women who took the second dose did not achieve the desired result.[38] In one other study that evaluated women using the proposed regimen through 63 days gestation, 16 of 863 women received a second dose of misoprostol, with an efficacy rate of 100 percent.[39] The other 7 studies had efficacy rates for an additional dose of misoprostol ranging from 67 percent to 100 percent.[40]

[36]E.G. Raymond and D.A. Grimes, "The Comparative Safety of Legal Induced Abortion and Childbirth in the United States," *Obstetrics & Gynecology,* vol. 119 (2012): 215-219.

[37]M.F. Reeves, A. Kudva, and M. Creinin, "Medical Abortion Outcomes after a Second Dose of Misoprostol for Persistent Gestational Sac," *Contraception*, vol. 78 (2008): 332-335.

[38]Boersma, Meyboom-de Jong, and Kleiverda, "Mifepristone Followed by Home Administration of Buccal Misoprostol," 61-66.

[39]K.S. Louie, T. Tsereteli, E. Chong, F. Ailyeva, G. Rzayeva, and B. Winikoff, "Acceptability and Feasibility of Mifepristone Medical Abortion in the Early First Trimester in Azerbaijan," *The European Journal of Contraception & Reproductive Health Care,* vol. 19, no. 6 (2014): 457-464.

[40]Mifeprex's sponsor noted to FDA that approximately 1 percent to 5 percent of women will need a second dose of misoprostol following the initial Mifeprex dosing regimen.

- **Follow-up care requirements.** FDA reviewed 11 studies that evaluated different methods for follow-up care after Mifeprex administration. One of these studies, which FDA considered a key publication on this topic, was a review of studies that assessed the impact of the timing of follow-up care.[41] This study found no differences in the failure rates between women who received follow-up care within one week of taking mifepristone compared to those who received follow-up care a week or more after taking mifepristone. The other 10 studies included a variety of study designs and dosing regimens through 63 days gestation, and FDA determined that the various methods of follow up, including home pregnancy testing and phone contact with the patient to inquire about symptoms, were acceptable alternatives to an in-clinic follow up.
- **Change in provider qualifications.** FDA reviewed four studies that addressed the efficacy of medical abortion performed by nonphysician health care providers; three of which used the proposed dosing regimen and one evaluated vaginal administration of misoprostol.[42] In these studies, almost 1,500 women had gestations through 70 days or more, and over 700 of these women had nonphysician care. In addition, almost 2,300 women had gestations up to 63 days, and over 1,000 of these women had nonphysician care. The efficacy rates were greater than or equal to 96 percent across all of the studies, regardless of gestational age or provider type.

FDA also received three letters from representatives of advocacy organizations and professional associations—some of which were signed by more than one entity—requesting that FDA revise the Mifeprex labeling in a manner that would reflect then-current clinical practice,

[41]E.G. Raymond, et al., "First-Trimester Medical Abortion with Mifepristone 200 mg and Misoprostol: A Systematic Review," *Contraception,* vol. 87 (2013): 26-37.

[42]The three studies that used the proposed regimen were (1) H. Kopp Kallner, R. Gomperts, E. Salomonsson, M. Johansson, L. Marions, and K. Gemzell-Danielsson, "The Efficacy, Safety and Acceptability of Medical Termination of Pregnancy Provided by Standard Care by Doctors or by Nurse-Midwives: A Randomized Controlled Equivalence Trial," *BJOG: An International Journal of Obstetrics and Gynaecology*, vol. 122 (2015): 510-517; (2) Olavarrieta, Ganatra, Sorhaindo, Karver, Seuc, Villalobos, Garcia, Pérez, Bousieguez, and Sanhueza, "Nurse Versus Physician-Provision of Early Medical Abortion," 249-258; and (3) M. Puri, A. Tamang, P. Shrestha, D. Joshi, "The Role of Auxiliary Nurse-Midwives and Community Health Volunteers in Expanding Access to Medical Abortion in Rural Nepal," *Reproductive Health Matters,* vol. 44 Supplement (2015): 94-103. The study that addressed vaginal misoprostol was: I.K. Warriner, D. Wang, N.T.M. Huong, K. Thapa, A. Tamang, I. Shah, et al., "Can Midlevel Health-Care Providers Administer Early Medical Abortion as Safely and Effectively as Doctors? A Randomized Controlled Equivalence Trial in Nepal," *Lancet,* vol. 377 (2011): 1155-1161.

including the new dosing regimen and extending the gestational age limit through 70 days.[43] Among others, the signers of these letters included the American Congress of Obstetricians and Gynecologists, American Public Health Association, Gynuity Health Projects, Ibis Reproductive Health, and National Abortion Federation. FDA officials told us that the peer-reviewed studies the agency received from external entities (i.e., entities other than Mifeprex's sponsor) were also submitted by Mifeprex's sponsor in the supplemental application, which FDA reviewed.[44] In addition, FDA officials told us that they received letters from organizations that were based on other than scientific perspectives, and FDA officials noted that they only considered scientific information in their review of the Mifeprex supplemental application.

FDA Evaluated Safety Information and Adverse Event Data as Part of Its Assessment of the Proposed Changes to the Mifeprex Labeling

FDA also reviewed published studies submitted by the drug's sponsor to assess the safety profile of the proposed dosing regimen, including both U.S. and international studies. Of the seven U.S. studies submitted with the Mifeprex supplemental application that examined safety issues, one specifically addressed deaths associated with Mifeprex.[45] This study noted that there were no deaths among 578 patients who received the proposed Mifeprex dosing regimen through 63 days gestation. According to FDA, because only one of these studies addressed deaths associated with Mifeprex, this may reflect the fact that it is a rare outcome and, therefore, the absence of reported deaths might not be noted by the authors of a study. In addition, FDA reviewed an observational study from Australia that was also submitted as part of the application. It identified one death from sepsis—a life-threatening complication of an infection—

[43]According to FDA, once the agency approves a drug, health care providers generally may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient, a practice known as off-label use. FDA also indicated that the proposed changes approved in the Mifeprex supplemental application were consistent with current medical practice.

[44]According to FDA officials, the agency received one study from an external entity that was superseded by a more current publication on the same topic by one of the same authors. In this instance, FDA officials reviewed the more current publication provided by Mifeprex's sponsor.

[45]D. Grossman, K. Grindlay, T. Buchacker, K. Lane, and K. Blanchard, "Effectiveness and Acceptability of Medical Abortion Provided through Telemedicine," *Obstetrics & Gynecology,* vol. 118 (2011): 296-303.

among 13,345 pregnancy terminations using the proposed dosing regimen through 63 days gestation.[46]

In addition to reviewing published studies submitted by Mifeprex's sponsor, FDA reviewed adverse event reports from the drug's approval on September 28, 2000, through November 17, 2015. During this time, there were 17 reported deaths in the United States associated with Mifeprex, and 8 of those were associated with sepsis. Seven of the 8 sepsis cases were associated with vaginal use of misoprostol, which was, but no longer is, a common practice, according to FDA. The agency found that the adverse event data that it reviewed demonstrated that the rates of hospitalizations, severe infections, blood loss requiring transfusion, and complications related to ectopic pregnancy remained stable and acceptably low.

FDA also reviewed common adverse events, such as nausea, vomiting, diarrhea, and fever/chills, reported in U.S. and international studies submitted by Mifeprex's sponsor, and found the reporting of the frequencies of these events was higher in the U.S. studies. However, FDA determined that these differences likely reflected lower reporting of adverse events in international studies. These common adverse events are included in the Mifeprex labeling. The labeling also cites bleeding and cramping, which are expected effects of the drug regimen, according to FDA. Overall, FDA found the rate of deaths and nonfatal serious adverse events associated with Mifeprex to be acceptably low, and data for the proposed regimen did not suggest a safety profile that deviated from that of the originally approved Mifeprex regimen, which was approved as part of an application with restrictions to assure safe use. In addition, no association between adverse outcomes and increasing gestational age was identified.

In January 2016, FDA completed a review of adverse event data associated with Mifeprex in its FAERS database, as well as the published medical literature, on a potential safety concern regarding anaphylaxis and angioedema associated with mifepristone.[47] FDA's review of FAERS data found one case of anaphylaxis and six cases of angioedema with

[46]P. Goldstone, J. Michelson, and E. Williamson, "Early Medical Abortion Using Low-Dose Mifepristone Followed by Buccal Misoprostol: A Large Australian Observational Study," *Medical Journal of Australia,* vol. 197 (2012): 282-286.

[47]Anaphylaxis is a severe, potentially life-threatening allergic reaction. Angioedema is a form of severe swelling beneath the skin's surface.

mifepristone administration, with six of the seven cases seen in women using mifepristone for pregnancy termination, as opposed to using mifepristone for Cushing's syndrome.[48] The sole case of anaphylaxis could not be directly attributed to mifepristone because an oral antibiotic (doxycycline) was concomitantly administered, according to FDA. FDA did not find any additional cases of anaphylaxis or angioedema with mifepristone administration in its review of the literature. FDA noted that anaphylaxis was included in the current labeling for misoprostol. Because the approved Mifeprex regimen includes misoprostol, FDA determined that the Mifeprex labeling should also be updated to include anaphylaxis, despite the lack of anaphylaxis cases with mifepristone alone. The addition of angioedema was supported by the FAERS data documented in FDA's review. As a result, anaphylaxis and angioedema were added to the areas of the Mifeprex labeling that address allergic reactions.

The potential risk of uterine rupture was also considered in FDA's review of the Mifeprex supplemental application. FDA reviewers conducted a literature search on this topic, and identified five reports of uterine rupture in studies published from 2000 through 2014; three of which occurred with the combined mifepristone/misoprostol dosing regimen. FDA also completed a review of FAERS from January 1, 1965, through October 15, 2015, for reports of uterine rupture.[49] Of the 80 reports found in FAERS, 77 cited use of misoprostol alone, and 3 cited use of both mifepristone and misoprostol. Two reports of uterine rupture in the first trimester were identified in the FAERS review, both using misoprostol alone. One report entailed an unspecified dose and route of misoprostol at 5 weeks gestation. The other report involved vaginal administration of 800 micrograms of misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar. Information regarding this safety concern was added to the Mifeprex labeling when the supplemental application was approved on March 29, 2016. The agency concluded, however, that no restriction of use was needed, because this was an extremely rare adverse event.

FDA concluded that the evidence it reviewed and evaluated, including the revisions to the REMS, demonstrated acceptable safety for the proposed

[48]Cushing's syndrome is a hormonal disorder affecting both men and women caused by prolonged exposure of the body's tissues to high levels of the hormone cortisol. Mifepristone is also approved for this indication, under the brand name Korlym.

[49]According to FDA, January 1, 1965, is the date that the FAERS predecessor system was initiated.

changes to the Mifeprex regimen, and that the dosing regimen had a similar safety profile as the original regimen approved in 2000. The agency further concluded that adverse events of interest—such as deaths, serious infection, transfusions, ectopic pregnancies, and uterine rupture—remained rare, and were not necessarily attributable to Mifeprex use.[50]

FDA's Monitoring Activities Have Not Identified Significant Safety Concerns with Mifeprex; Stakeholders' Views on FDA's Monitoring and the Drug's Safety Were Mixed

FDA's monitoring of Mifeprex—primarily through inspections, and review and analysis of adverse event data—has not identified any significant concerns with the safety and use of Mifeprex. The views of the stakeholder organizations that we contacted regarding FDA's monitoring of the safety of Mifeprex and the safety of the drug itself were mixed.

FDA's Monitoring Has Not Identified Any Significant Concerns Regarding the Safety and Use of Mifeprex as Marketed with the Approved REMS

Since our prior report was issued in 2008, FDA conducted three postmarketing adverse drug experience inspections of Mifeprex's sponsor—in 2010, 2014, and 2016.[51] It identified minor deficiencies, but no significant safety concerns. These inspections each contained between two and four inspection observations—that is, the investigator observed conditions that, in his or her judgment, constituted violations of applicable federal requirements. In each of these inspections, FDA's final classification was "voluntary action indicated," meaning that objectionable conditions or practices were found, but they did not meet the threshold of regulatory significance. According to agency officials, FDA's practice for

[50]Similarly, a recently issued study by the National Academies of Sciences, Engineering, and Medicine reported that complications—such as hemorrhage, hospitalization, persistent pain, infection, or prolonged heavy bleeding—are rare after a medical abortion. This study cited some of the same studies FDA relied on and noted that complications occur in no more than a fraction of a percent of patients. National Academies of Sciences, Engineering, and Medicine, *The Safety and Quality of Abortion Care in the United States* (Washington, D.C.: prepublication copy).

[51]See GAO-08-751.

inspections resulting in this classification is to review the corrective actions taken by the establishment related to the objectionable conditions or practices during the course of the next regularly scheduled inspection. FDA officials told us that they have not yet scheduled the next postmarketing adverse drug experience inspection.

According to FDA, violations associated with postmarketing adverse drug experience inspections classified as voluntary action indicated are typically technical in nature. Examples of some of the observations from inspections of Mifeprex's sponsor include the following:

- In 2010, the sponsor was found to have used an older version of the form used for mandatory reporting of adverse events (FDA Form 3500A), rather than the more recent version.
- In 2014, two serious adverse events were not reported to FDA within the required 15-day period, and instead were included in the sponsor's subsequent quarterly adverse event report to FDA.
- In 2016, the sponsor's quarterly adverse event reports did not include the required analysis of the Postmarketing 15-day Alert Reports that occurred over the period.

In addition to postmarketing adverse drug experience inspections, Mifeprex's sponsor was subject to a REMS compliance inspection, which the agency conducted in 2014. According to FDA officials, the agency did not identify any compliance issues and determined that the final classification was no action indicated.

FDA also conducted three inspections since 2008 of the facility where Mifeprex is manufactured to ensure compliance with current good manufacturing practices. FDA did not find any deficiencies during two of these inspections; however, in the other inspection, FDA's findings resulted in a final classification of voluntary action indicated. According to the inspection report, FDA officials found an improperly performed test on a raw material used in another product produced at the same facility, not related to Mifeprex. A subsequent inspection determined that corrective action was taken by the manufacturer.

In addition to inspection data, FDA conducted ongoing monitoring of adverse event data. These data are collected through required reporting, including periodic reports on adverse events provided by the sponsor and reports by the prescriber to the sponsor, which, depending on the event, may be required under the REMS. In addition, voluntary reports may be made by the public. FDA compiled this information into periodic

postmarketing adverse event summary reports, the interval of which ranged from 2 to 18 months. These reports show that between September 28, 2000, and June 30, 2017, there were approximately 4,200 reports of adverse events associated with Mifeprex, including approximately 1,000 hospitalizations and 20 deaths.[52] These deaths represented a reporting rate of 0.0006 percent for the approximately 3.2 million women who have used Mifeprex since 2000. For context, a study of mortality among women who did not have an abortion and proceeded to a live birth estimated a mortality rate of 0.009 percent. Nonfatal adverse events, including blood loss requiring transfusion and infections, were more common among women who took Mifeprex, but still relatively low compared to the number of users. (See table 2.)

[52]Mifeprex's sponsor reported two additional deaths to FDA that had not yet been included in FDA's periodic adverse event report—one reported in September 2017 and one reported in December 2017. FDA gathers and reports data on adverse events associated with Mifeprex, which are not necessarily caused by Mifeprex. For example, an unrelated health condition observed near the time that a woman took Mifeprex may be included in FDA's adverse event summary data.

Table 2: Adverse Events Associated with Mifeprex Reported to FDA from September 28, 2000, through June 30, 2017

	September 28, 2000 to October 31, 2012[a]	November 1, 2012 to June 30, 2017[a]
Adverse event category	**Number of cases**	**Number of cases**
Any adverse event[b]	2,740	1,439
Specific types of adverse events[c]		
Deaths[d]	14	6
Hospitalization	768	273
Blood loss with transfusion	416	182
Infections	308	103
Ectopic pregnancies	66	31
Severe infections	57	12

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-18-292

Notes: (1) Approximately 3.2 million women have taken Mifeprex since its initial approval in 2000. (2) An adverse event associated with Mifeprex does not necessarily indicate that Mifeprex caused the event.

[a]FDA implemented the FDA Adverse Event Reporting System (FAERS) in 2012, and migrated all the data from the previous reporting system to FAERS. Adverse event summary reports beginning on November 1, 2012, are based on FAERS data. Differences may exist when comparing case counts in FAERS with FDA's previous reporting system. Therefore, FDA does not recommend calculating a cumulative number for the data in table 2, with the exception of the case counts for deaths and ectopic pregnancies. These data were harmonized by FDA and may be added.

[b]Any adverse event includes all the categorized adverse events listed below it (i.e., deaths, hospitalization, blood loss with transfusion, infections and severe infections, and ectopic pregnancies), as well as other noncategorized events.

[c]Of the six types of categorized adverse events, only deaths are solely recorded as such—that is, they are not reflected in the tally for other categorized adverse events. The remaining categories are overlapping, meaning that a single case could be counted within multiple categories. Also, the hospitalization category includes both categorized and noncategorized adverse events. According to FDA, the most common adverse events among those that are not categorized (accounting for approximately 94 percent) are vaginal bleeding not requiring transfusion, retained products of conception, ongoing pregnancy, cramping, dizziness, and nausea. Among noncategorized adverse events resulting in hospitalization, the most common is dilation and curettage (accounting for approximately 81 percent).

[d]In addition to the 20 deaths included in FDA's periodic adverse event reports, the sponsor reported two additional deaths to FDA—one reported in September 2017 and one reported in December 2017—which the agency said will be included in its next periodic adverse event report.

Although postmarketing study commitments or requirements are another method for obtaining additional information about drug safety and use, in the case of Mifeprex the planned studies were deemed by FDA to be infeasible. As we previously reported, FDA originally approved Mifeprex subject to the sponsor's commitment to conduct two postmarketing studies.[53] For the first study, the sponsor agreed to assess whether

[53]See GAO-08-751.

clinical outcomes were similar for patients under the care of providers who possessed the surgical intervention skills to perform a surgical abortion compared with patients of providers who did not have such skills and referred patients for surgical abortions. FDA said the sponsor reported that the number of physicians who prescribed Mifeprex and did not possess the surgical intervention skills to perform a surgical abortion was so small that such a study was not feasible. FDA agreed and released them from that commitment in September 2008. For the second study, the sponsor was required to examine, through a surveillance and reporting system, the outcomes of pregnancies where the drug regimen failed to result in their termination. According to FDA officials, Mifeprex's sponsor reported to FDA that over nearly 2 years of monitoring (January 2006 through November 2007) there were one or two instances per year of the drug not resulting in termination. The sponsor told FDA that this was, in part, because patients had to consent to being monitored, resulting in a very small number of participants. Given these low numbers, FDA agreed that this study was also not feasible.

We also found that FDA's Sentinel System, which was developed to enhance the agency's ability to monitor postmarketing safety, is not a viable option for monitoring the use of Mifeprex. Although it contains millions of records, the Sentinel System is based on administrative and claims data, and only reimbursed health care encounters, procedures, and medications are captured in the system. Because of the REMS restrictions placed on the drug's distribution, Mifeprex is not dispensed in pharmacies. Instead, it is only available under certain conditions and from certain clinics, medical offices, and hospitals. Therefore, according to FDA officials, the Sentinel System does not include a sufficient number of Mifeprex dispensings to generate valid results. Nonetheless, we asked FDA to query the Sentinel System for mifepristone (the active pharmaceutical ingredient for Mifeprex) beginning in 2000, when the drug was first approved. The results of this query showed that, until 2012, mifepristone registered a small number of drug dispensings. Specifically, between 2000 and 2011, only 12 individuals were identified as potentially exposed to mifepristone. However, from 2012 through 2016, 243 individuals were identified, including both men and women. FDA officials explained that another drug—Korlym, which treats Cushing's syndrome and contains the same active pharmaceutical ingredient as Mifeprex—

became available in 2012.[54] Even with additional dispensings beginning in 2012, FDA officials said there were still insufficient data captured to enable a robust safety assessment.

Stakeholder Organizations Had Mixed Views on FDA's Monitoring of Mifeprex and of Mifeprex's Safety

The views of the stakeholder organizations that provided us with information on FDA's monitoring of the safety and use of Mifeprex, and the safety of the drug itself, were mixed. Stakeholders provided positive comments regarding FDA's monitoring of Mifeprex and also made suggestions to improve what they considered to be weaknesses. Positive comments included that

- FDA had a very comprehensive monitoring program that mandated the reporting of serious adverse events associated with Mifeprex up through 2016. In light of the low rates of nonfatal adverse events and the good safety profile of Mifeprex, FDA no longer requires providers to report nonfatal adverse events.
- FDA is properly monitoring the safety and use of Mifeprex through a robust adverse event reporting system, and FDA is doing its due diligence, based on the agency's mission, to identify any safety issues with the drug.
- FDA's requirement that Mifeprex be subject to a REMS has made it more likely that adverse events would be reported. Specifically, additional contacts with health care providers, as is required by the Mifeprex REMS in the form of prescriber certification and patient education, generally lead to higher adverse event reporting rates than drugs without such requirements.

Stakeholders that either commented that FDA's monitoring efforts could be improved or that expressed concern about the agency's ability to know the extent of potential safety issues said, for example, that

- FDA may only be aware of a fraction of adverse events associated with Mifeprex. There are anecdotal examples of adverse events, such as severe bleeding, that may not be reported as such or that may be interpreted by emergency health care providers as a natural

[54]The analysis that was conducted in the Sentinel System only recognizes the active pharmaceutical ingredient and does not distinguish between the drugs dispensed, according to FDA officials. The data show both men and women receiving mifepristone since 2012. Korlym's dose of mifepristone is significantly higher than that of Mifeprex and, unlike Mifeprex, the drug is taken by patients on an ongoing basis.

miscarriage. Underreporting may get worse under the revised Mifeprex label, which eliminates the follow-up visit and does not require prescribers to report nonfatal adverse events.

- FDA may not have reliable data on the number of women who have used Mifeprex, which would affect the denominator for tracking adverse events. With an unclear denominator, FDA may not have an accurate measure of adverse event rates associated with Mifeprex.

Regarding the safety of Mifeprex, stakeholders we contacted provided a mix of favorable comments about the drug, as well as certain safety concerns. Positive comments included the following

- The mortality rate associated with Mifeprex is extremely low—about one fourteenth the mortality rate associated with live birth.
- Nonfatal serious adverse events following Mifeprex use, such as hospital admission, blood transfusion, or serious infection, are also rare, occurring at rates ranging from 0.01 percent to 0.7 percent, and are almost always treatable without permanent effects. Side effects, such as bleeding, cramping, fever, and chills, are typically minor and transient.
- In the years since mifepristone's approval, multiple clinical trials, dozens of studies, and extensive experience across the globe have confirmed FDA's finding that mifepristone is a safe and reliable method of abortion. Thus, any significant concern about the safety of Mifeprex would be unwarranted.

Stakeholders also expressed some concerns about Mifeprex's safety. For example, they reported that

- Mifeprex may be linked to hemorrhaging and serious infections. A study was cited that showed adverse events were more likely to be associated with a medical abortion rather than a surgical abortion.[55] Two other studies were cited that examined the effect mifepristone may have on the body's ability to control hemorrhaging and prevent

[55]M. Niinimäki, et al., "Immediate Complications after Medical Compared with Surgical Termination of Pregnancy," *Obstetrics & Gynecology,* vol. 114, no. 4 (October 2009): 795-804. This study of over 42,000 women in Finland who had abortions from 2000 to 2006 found that, overall, medical abortion had roughly four times the rate of adverse events than surgical abortion, and hemorrhaging was experienced by 16 percent of medical abortion patients compared with 2 percent of surgical abortion patients.

serious infections.[56] For example, one of the studies found that serious bacterial infection and sepsis may occur without the usual signs of infection with the use of mifepristone for medical abortion.

- Safety issues may be exacerbated by the Mifeprex labeling changes. For example, a study was cited that found that the rates of pregnancy termination with Mifeprex dropped from 92 percent up to the 7th week of gestation to 77 percent at the 9th week.[57]
- Women in the later weeks of pregnancy who live far from a health care provider may be at increased risk of serious hemorrhaging under the revised labeling, which does not require a second visit with a health care provider.

In addition, another comment we heard was that the agency was being too restrictive by continuing to require a REMS for the drug. Specifically, we were told that Mifeprex should not continue to be restricted to being dispensed at a clinic, medical office, or hospital—as it is under the Mifeprex REMS—because ample research shows Mifeprex to be safe and adverse events to be rare. Stakeholders also noted that women in rural areas may have less access to the drug, and Mifeprex's sponsor commented that the distribution restrictions likely result in the drug being less accessible than it otherwise would be.[58]

In response to the concerns regarding Mifeprex that we heard from stakeholder organizations, FDA officials said that the agency approved the supplemental application for Mifeprex under the same approval standards that it applies to all new drug applications and supplemental applications, and found that the data and information submitted in the supplemental application demonstrated that Mifeprex is safe and effective

[56]R.P. Miech, "Pathopharmacology of Excessive Hemorrhage in Mifepristone Abortions," *Annals of Pharmacotherapy,* vol. 41, no. 12 (December 2007): 2002-2007. See also, R.P. Miech, "Pathophysiology of Mifepristone-induced Septic Shock due to *Clostridium sordellii*," *Annals of Pharmacotherapy,* vol. 39, no. 9 (September 2005): 1483-1488.

[57]I. M. Spitz, C. W. Bardin, L. Benton, and A. Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," *New England Journal of Medicine,* vol. 338, no. 18 (Apr. 30, 1998): 1241-1247.

[58]In October 2017, a doctor and several professional health associations filed a lawsuit in the U.S. District Court for the District of Hawaii to challenge the distribution restrictions imposed by FDA under the Mifeprex REMS. Chelius, et al. v. Wright, No. 17-cv- 00493 (D. Hawaii, filed Oct. 3, 2017). Plaintiffs argued that REMS requirements may be imposed only when necessary to ensure that a drug's benefits outweigh its risks, and that restrictions requiring Mifeprex to be distributed through clinics or hospitals do not meet the criteria.

for its intended use. FDA officials noted that Mifeprex also has a REMS in place to ensure safety. They also stressed that, as with all FDA-approved drugs, Mifeprex is subject to adverse event reporting requirements and continued postmarketing safety monitoring by the agency.

Agency Comments

We provided a draft of this report for comment to HHS. HHS provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the Secretary of Health and Human Services, appropriate congressional committees, and other interested parties. In addition, the report will be available at no charge on the GAO Web site at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs are on the last page of this report. GAO staff who made major contributions to this report are listed in appendix I.

Marcia Crosse
Director, Health Care

List of Requesters

The Honorable Robert Aderholt
Chairman
Subcommittee on Agriculture, Rural Development,
Food and Drug Administration, and Related Agencies
Committee on Appropriations
House of Representatives

The Honorable Tom Cole
House of Representatives

The Honorable Chuck Fleischmann
House of Representatives

The Honorable Jeff Fortenberry
House of Representatives

The Honorable Tom Graves
House of Representatives

The Honorable Andy Harris
House of Representatives

The Honorable Steven Palazzo
House of Representatives

The Honorable Kevin Yoder
House of Representatives

Appendix I: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse (202) 512-7114 or crossem@gao.gov

Staff Acknowledgments

In addition to the contact above, Geri Redican-Bigott (Assistant Director), Lisa A. Lusk (Analyst-in-Charge), George Bogart, Drew Long, and Perry Parsons made key contributions to this report. Kaitlin Farquharson also made contributions to this report.

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Public Affairs	Chuck Young, Managing Director, youngc1@gao.gov, (202) 512-4800 U.S. Government Accountability Office, 441 G Street NW, Room 7149 Washington, DC 20548
Strategic Planning and External Liaison	James-Christian Blockwood, Managing Director, spel@gao.gov, (202) 512-4707 U.S. Government Accountability Office, 441 G Street NW, Room 7814, Washington, DC 20548

BACK

SEAL AREA FOR LOT & EXP
25 mm x 4.5 mm

AREA FOR LOT AND EXP
TO BE PRINTED IN DARK COLOR
26 mm x 5.5 mm

000067194

DRUG FACTS TEXT DEFINED	TYPE SIZE
• HEADINGS	4.75 pt
• SUBHEADINGS/BODY TEXT	4.75 pt
• LEADING	4.75 pt
• BULLETS	3.75 pt
• SPACE BEFORE BULLET	2 ems
• WARNING BOX LINE, HAIRLINES	N/A

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

LIFT HERE

Drug Facts

Active ingredient (in each tablet) — **Purpose**

Ibuprofen 200 mg (NSAID)* ..... Pain reliever/ Fever reducer

*nonsteroidal anti-inflammatory drug

Uses

- temporarily re ieves minor aches and pains due to:
  - headache
  - toothache
  - backache
  - menstrual cramps
  - the common cold
  - muscular aches
  - minor pain of arthritis
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

Drug Facts (continued)

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

PANEL 1

Drug Facts (continued)

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if

- stomach bleeding warning applies to you
- you have problems or serious side effects from taking pain relievers or fever reducers
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
- you are taking a diuretic

Ask a doctor or pharmacist before use if you are

- under a doctor's care for any serious condition
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs

Drug Facts (continued)

Stop use and ask a doctor if

- you experience any of the following signs of stomach bleeding:
  - feel faint
  - vomit blood
  - have bloody or black stools
  - have stomach pain that does not get better
- you have symptoms of heart problems or stroke:
  - chest pain
  - trouble breathing
  - weakness in one part or side of body
  - slurred speech
  - leg swe ling
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear

PANEL 2

Drug Facts (continued)

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen at 20 weeks or later in pregnancy unless definitely directed to do so by a doctor because t may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- adults and children 12 years and over: take 1 tablet every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 tablet, 2 tablets may be used
- do not exceed 6 tablets in 24 hours, unless directed by a doctor
- ch ldren under 12 years: ask a doctor

Drug Facts (continued)

Other information

- read all warnings and directions before use. Keep carton.
- store at 20-25°C (68-77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients

acetylated monoglycerides, colloidal silicon dioxide, corn starch, croscarmellose sodium, methylparaben, microcrystalline cellulose, pharmaceutical glaze, pharmaceutical ink, povidone, pregelatinized starch, propylparaben, sodium benzoate, sodium lauryl sulfate, stearic acid, sucrose, synthetic iron oxide, titanium dioxide, white wax

Questions or comments?

call toll free **1-800-88-ADVIL**

000067196

BASE PANEL

000067196

DRUG FACTS TEXT DEFINED	TYPE SIZE
• DRUG FACTS TITLE	9 pt
• DRUG FACTS CONTINUED	8 pt
• HEADINGS	8 pt
• SUBHEADINGS/BODY TEXT	6 pt
• LEADING	6.5 pt
• # OF CHARACTERS PER INCH	<39
• BULLETS	5 pt
• SPACE BEFORE BULLET	2 ems
• BARLINES, HAIRLINES	1.5 pt, .5 pt
• SPACE BETWEEN HAIRLINES AND BOX END	2 spaces

UNVARNISHED AREA
FOR LOT & EXP. DATE

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DRUG FACTS TEXT DEFINED	TYPE SIZE
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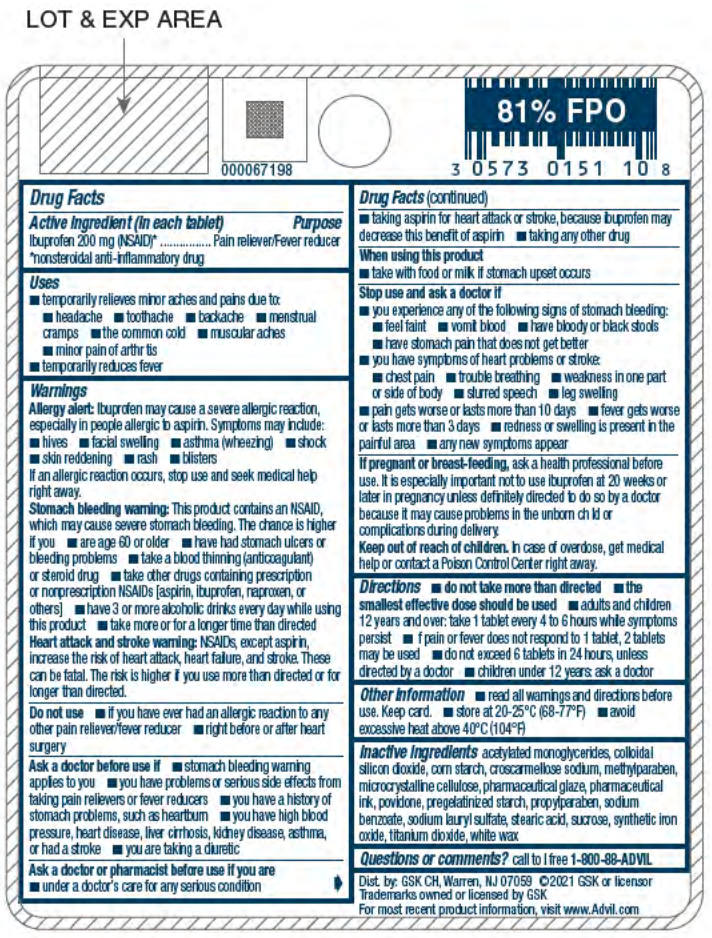
• DRUG FACTS CONTINUED	8 pt
• HEADINGS	8 pt
• SUBHEADINGS/BODY TEXT	6 pt
• LEADING	6.5 pt
• # OF CHARACTERS PER INCH	<39
• BULLETS	5 pt
• SPACE BEFORE BULLET	2 ems
• BARLINES, HAIRLINES	1.5 pt, .5 pt
• SPACE BETWEEN HAIRLINES AND BOX END	2 spaces

FRONT



BACK

000067198

DRUG FACTS MODIFIED TEXT DEFINED	TYPE SIZE
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• DRUG FACTS CONTINUED	7 pt
• HEADINGS	7 pt
• SUBHEADINGS/BODY TEXT	6 pt
• LEADING	6.25 pt
• # OF CHARACTERS PER INCH	<39
• BULLETS	5 pt
• SPACE BEFORE BULLET	2 ems
• BARLINES, HAIRLINES	1.5 pt, .5 pt
• SPACE BETWEEN HAIRLINES AND BOX END	2 spaces

	severity of moderate to severe VMS when compared with placebo at Weeks 4 and 12 Endometrial hyperplasia: Determine if TX-001HR given daily is effective at achieving a ≤ 1% incidence rate of endometrial hyperplasia following 12 months of therapy		• 0.5 mg estradiol and 100 mg progesterone daily • 0.5 mg estradiol and 50 mg progesterone daily • 0.25 mg estradiol and 50 mg progesterone daily Oral Placebo daily	726 analyzed Safety: 1835 enrolled postmenopausal women 40 to 65 years of age 1275 completers	

Source: Adapted from NDA 210132, Submodule 2.7.6 Synopsis of Individual Studies, Table 1.
Abbreviations: BA – bioavailability; PK – pharmacokinetics; BE – bioequivalence; VMS – vasomotor symptoms.

5.2. Review Strategy

The available clinical data in primary 52-week, phase 3, safety and efficacy clinical Trial TXC12-05 (first 12-weeks placebo-controlled) provide the basis for consideration regarding the efficacy of TX-001HR (combined 1.0 mg estradiol plus 100 mg progesterone, (b) (4) oral capsules for the treatment of moderate to severe vasomotor symptoms, due to menopause.

Trial TXC12-05 is the single safety and efficacy trial conducted in support of moderate to severe vasomotor symptoms and, is the single safety trial conducted in support of general and endometrial safety and long-term drug exposure data for this combined estradiol plus progesterone product for use in a postmenopausal woman with a uterus.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial TXC12-05

6.1.1. Study Design

Overview:
TherapeuticsMD has developed an oral combination product (TX-001HR) consisting of a softgel formulation containing solubilized estradiol with micronized progesterone intended to treat moderate to severe vasomotor symptoms while protecting the endometrium from unopposed

estradiol. The product is comprised of active ingredients of estradiol and progesterone that are chemically identical to endogenous estradiol and progesterone in a softgel capsule form. The rationale for the development of TX-001HR, per the applicant, is to provide postmenopausal women with an FDA-approved combination of estradiol and progesterone, and to "alleviate the need for unapproved compounded agents of estradiol and progesterone."

Postmenopausal women 40 to 65 years of age (at the time of randomization) who qualified per the inclusion and exclusion entry criteria were enrolled in Trial TXC12-05 after they provided written informed consent as described in 21 CFR 50.

A total of 117 clinical sites in the United States screened at least one subject and 111 clinical sites randomized at least one postmenopausal woman into either the vasomotor symptoms (VMS) subtrial (104 sites) or into the non-VMS subtrial (98 sites).

(b) (4) was responsible for processing the central laboratory samples including Papanicolaou (Pap) smears, and endometrial biopsies. (b) (4) was also responsible for the receipt and storage of hormone samples for estradiol, estrone, and progesterone. Hormone levels of estradiol, estrone, and progesterone were analyzed by (b) (4)

Electrocardiograms (ECGs) and mammograms were performed and read locally. The individual clinical site personnel entered the results of these tests directly into the eCRF.

Catalent Pharma Solutions and the (b) (4) were responsible for the packaging, distribution, resupply, storage and destruction of trial medication. Catalent was the primary vendor from approximately July 2013 through August 2014, at which time (b) (4) assumed primary responsibilities through trial completion.

Trial TXC12-05 Objectives:

Vasomotor symptoms: To determine whether TX-001HR given in a continuous fashion is effective at reducing the frequency and severity of moderate to severe VMS associated with menopause when compared with placebo at Weeks 4 and 12.

Endometrial hyperplasia: To determine whether TX-001HR given in a continuous fashion is effective at achieving a ≤ 1% incidence rate of endometrial hyperplasia following 12 months of therapy.

Trial Design for Phase 3 Trial TXC12-05:

Trial TXC12-05 was a phase 3, 52-weeks, multi-center (111 clinical sites randomized at least 1 postmenopausal woman), randomized, double-blind, placebo-controlled (first 12 weeks), parallel group trial (1 mg estradiol and 100 mg progesterone, 0.5 mg estradiol and 100 mg progesterone, 0.5 mg estradiol and 50 mg progesterone, 0.25 mg estradiol and 50 mg

progesterone, and placebo). The trial population consisted of non-hysterectomized postmenopausal women, 40 to 65 years of age, who met the trial entry criteria. During the Screening period, all trial participants were provided with a diary to self-assess the frequency and severity of their VMS. Trial participants who experienced a minimum daily frequency of ≥ 7 (or ≥ 50 per week) moderate to severe hot flushes participated in the VMS subtrial for the first 12 weeks of treatment (placebo-controlled). The VMS subtrial participants were stratified by treatment arm within the clinical sites, and only VMS subtrial participants had the possibility of being randomized to placebo.

Trial participants who otherwise qualified for the trial except for reporting the required minimum daily frequency of moderate to severe hot flushes were stratified by treatment arm within clinical sites to one of four active treatment arms and received blinded trial medication for 12 months. These participants did not participate in the VMS subtrial.

Treatments Administered:
Randomized trial participants self-administered orally one of the following four arms of active TX-001HR treatment daily at bedtime with food for 12 months. Two different sizes of capsules were necessary to accommodate the different doses. To maintain the trial blind, the trial had a double-blind, double-dummy treatment. Women randomized to active treatment took a placebo capsule matching the alternate capsule size from their active treatment. Two sizes of placebo capsules that were an identical match to the active medication, but without the estradiol and progesterone, were taken orally by women participating in the VMS subtrial that were randomized to placebo.

Treatment 1:	Combined 1 mg estradiol/100 mg progesterone [large active; small placebo]
Treatment 2:	Combined 0.5 mg estradiol/100 mg progesterone [large active; small placebo]
Treatment 3:	Combined 0.5 mg estradiol/50 mg progesterone [large placebo; small active]
Treatment 4:	Combined 0.25 mg estradiol/50 mg progesterone [large placebo; small active]
Treatment 5:	Placebo [large placebo; small placebo]

All trial participants self-administer orally two capsules daily at bedtime with food for 12 months. Each trial participant was dispensed enough trial medication to last until the next scheduled visit, with allowance for visit windows. The participants were instructed to return the used and unused containers of trial medication in the original packaging to the trial site at Visits 2, 3, 4, 5, 6, and 7. Trial sites verified and documented compliance based on counts of dispensed/returned trial medication and any additional information reported by the participant (for example, lost capsules).

Following informed consent procedures, trial participants completed initial Screening procedures that included: demographics, medical/gynecological history, concomitant medications, physical examination (including height, weight, and body mass index [BMI] calculation), pregnancy test, vital signs, pelvic and breast examinations, laboratory measurements, 12-lead ECG, Pap smear, mammography, and endometrial biopsy.

Upon completion of the initial Screening procedures, all participants who met eligibility requirements to continue Screening were provided with a hot flush diary that was completed for the remainder of the Screening period. Participants were instructed to complete the diary daily by recording the number and severity of hot flashes in their diaries. A minimum of 14 consecutive days of completed hot flush diary data were required during the baseline assessment at Screening, and the consecutive days must have occurred within the last 14 days prior to Randomization (not counting the day of Randomization). The most recent seven (7) consecutive days of data prior to Randomization was used to determine the baseline number of mild, moderate, or severe hot flushes for each participant.

At Randomization, participants who continued to meet the eligibility criteria with a minimum daily frequency of ≥ 7 (or ≥ 50 per week) moderate to severe hot flashes in the seven days prior to Randomization (Visit 1) were randomized into the VMS subtrial. All other eligible participants not meeting the VMS subtrial hot flash requirements were randomized into the non-VMS portion of the trial.

All participants (both VMS subtrial and non-VMS subtrial) completed hot flash diaries and bleeding and spotting diaries through Week 12. After Week 12, all participants continued to complete bleeding and spotting diaries until the End-of-Trial (EOT) at Month 12.

Trial participants in the VMS subtrial completed Clinical Global Impression (CGI) questionnaires at Weeks 4, 8, and 12. The Menopause-Specific Quality of Life Questionnaire (MENQOL) and the Medical Outcomes Study-Sleep Questionnaire (MOS - Sleep) were administered at Randomization, Week 12, Month 6, and Month 12.

Vital signs and adverse event (AE) monitoring occurred throughout the trial; laboratory assessments were performed at Week 12, Month 6, Month 9, and Month 12 (or Early Termination).

Trial participants also had blood draws to assess hormone concentration levels at Screening for estradiol, estrone, and progesterone, additional draws at Week 4, Week 12, Month 6, Month 9, and Month 12 (or Early Termination) for estradiol and estrone, and at Week 12 and Month 12 (or Early Termination) for progesterone.

At Month 12 (or Early Termination), the following assessments were performed: physical examination (including weight), vital signs, pelvic and breast examinations, laboratory measurements, ECG, Pap smear, mammography, and endometrial biopsy.

The total duration of the study was approximately 14.5 months, which included a Screening period of approximately 60 days prior to randomization, approximately 12 months of treatment, and a 15-day follow-up period.

Clinical evaluations were performed at the following time points:

- Screening Period: Days -60 to 0
- Visit 1 (Randomization): Week 0, Day 1
- Visit 2 (Interim): Week 4, Day 28 (± 3 days)
- Visit 3 (Interim): Week 8, Day 56 (± 3 days)
- Visit 4 (Interim): Week 12, Day 84 (± 3 days)
- Visit 5 (Interim): Month 6, Day 180 (± 4 days)
- Visit 6 (Interim): Month 9, Day 270 (± 4 days)
- Visit 7 (End of Treatment): Month 12, Day 360 (± 4 days)
- Telephone Interview approximately 15 days after last dose

Inclusion Criteria:

For inclusion into the trial, postmenopausal women were required to fulfill all the following criteria:

1. Was a female between the ages of 40 and 65 years (at the time of Randomization) who was willing to participate in the trial, as documented by signing informed consent.
2. Was a postmenopausal woman with an intact uterus and a Screening serum estradiol level of ≤ 50 pg/mL. Postmenopausal was defined as:
    - ≥ 12 months of spontaneous amenorrhea, or
    - at least 6 months of spontaneous amenorrhea with a Screening serum follicle-stimulating hormone (FSH) level of > 40 mIU/ml, or
    - ≥ 6 weeks postsurgical bilateral oophorectomy
3. Was seeking treatment or relief for moderate to severe vasomotor symptoms associated with menopause.
4. To participate in the VMS subtrial, a trial participant must have reported ≥ 7 moderate to severe hot flushes per day, or ≥ 50 per week, at the Baseline assessment during Screening; trial participants whose hot flashes were less frequent were still able to participate as non-VMS subtrial participants.
5. Have a BMI ≤ 34 kg/m^2 (BMI values should be rounded to the nearest integer [for example, 34.4 rounds down to 34, while 26.5 rounds up to 27]).
6. Was willing to abstain from using products (other than trial medication) that contained estrogen, progestin, or progesterone throughout trial participation.

7. Was judged by the investigator as being in otherwise generally good health based on a medical evaluation performed during the Screening period prior to the initial dose of trial medication. The medical evaluation findings must have included:
    a) A normal or non-clinically significant physical examination, including vital signs (sitting blood pressure, heart rate, respiratory rate and temperature). Sitting systolic blood pressure of ≤ 140 mm Hg and diastolic blood pressure of ≤ 90 mm Hg at Screening. A participant could have been taking up to two antihypertensive medications.
    b) A normal or non-clinically significant pelvic examination.
    c) A mammogram that showed no sign of significant disease (may have been performed within previous 6 months prior to initial dose of trial medication). Women must have a breast imaging and reporting and database system (BI-RADS) 1 or 2 to enroll in the trial. An incomplete mammogram result, for example, BI-RADS 0, was not acceptable. The site obtained a copy of the official report for the woman's file, and verified that the mammogram itself was available if needed for additional assessment.
    d) A normal or non-clinically significant clinical breast examination. An acceptable breast examination was defined as no masses or other findings identified that were suspicious of malignancy.
    e) A normal Screening Pap smear. Participants with findings of atypical glandular cells (AGC), atypical glandular cells of undetermined significance (AGU)], atypical cells of undetermined significance (ASCUS) with high risk human papillomavirus (HPV) type upon reflex testing, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells of undetermined significance, cannot rule out HSIL (ASC-H]=), dysplastic cells, or malignant cells were excluded from Randomization.
    f) An acceptable result from an evaluable Screening endometrial biopsy. The endometrial biopsy reports by the two central pathologists at Screening must have each specified one of the following: proliferative endometrium; weakly proliferative endometrium; disordered proliferative pattern; secretory endometrium; endometrial tissue other (including benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc); endometrial tissue insufficient for diagnosis; no endometrium identified; or no tissue identified. At least one pathologist must have identified sufficient tissue to evaluate the biopsy. Additionally, the endometrial biopsy reports by the two central pathologists of Other Findings at Screening must have each specified one of the following: endometrial polyp not present; benign endometrial polyp; or polyp other.
    g) A normal or non-clinically significant 12-lead ECG.

Clinical Reviewer's Comments:

The inclusion criteria in Trial TXC12-05 were comprehensive and complete, and considered appropriate for this phase 3 clinical trial at the time of protocol review by DBRUP. For inclusion in VMS trials, we now recommend: 1) postmenopausal women with a body mass index (BMI) between 16 and 38 kg/m^2, and 2) sitting systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg.

Exclusion Criteria:

Any of the following was regarded as a criterion for exclusion from the trial:

1. Currently hospitalized.
2. A history of thrombosis of deep veins or arteries or a thromboembolic disorder.
3. A history of coronary artery or cerebrovascular disease (for example, myocardial infarction, angina, stroke, transient ischemic attack).
4. A history of a chronic liver or kidney dysfunction/disorder (for example, Hepatitis C or chronic renal failure).
5. A history of a malabsorption disorder (for example, gastric bypass, Crohn's disease).
6. A history of gallbladder dysfunction/disorders (for example, cholangitis, cholecystitis), unless gallbladder had been removed.
7. A history of diabetes, thyroid disease or any other endocrinological disease (participants with diet-controlled diabetes or controlled hypothyroid disease at Screening were not excluded).
8. A history of estrogen-dependent neoplasia; atypical ductal hyperplasia of the breast.
9. A finding of clinically significant uterine fibroids at Screening.
10. Had a uterine ablation.
11. Had a history of undiagnosed vaginal bleeding.
12. Had any history of endometrial hyperplasia, melanoma, or uterine/endometrial, breast or ovarian cancer.
13. Had a history of other malignancy within the last 5 years, with the exception of basal cell (excluded if within 1 year) or non-invasive squamous cell (excluded if within 1 year) carcinoma of the skin
14. Had a history of any other cardiovascular, hepatic, renal, pulmonary, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, psychological (for example, bipolar disorder, schizophrenia, major depressive disorder), or musculoskeletal disease or disorder that was clinically significant in the opinion of the investigator.
15. Had any of the following clinical laboratory values at Screening:
    a) fasting triglyceride of ≥ 300 mg/dL and/or total cholesterol of ≥ 300 mg/dL
    b) positive laboratory finding for Factor V Leiden mutation
    c) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1.5 times the upper limit of normal
    d) fasting glucose > 125 mg/dL
16. Was pregnant or had a positive urine pregnancy test.

17. Had contraindication to estrogen and/or progestin therapy or allergy to the use of estradiol and/or progesterone or any components of the trial medication.
18. Used 15 or more cigarettes per day or currently use any electronic cigarettes.
19. Had a history of drug and/or alcohol abuse within one year of start of trial.
20. Had used, within 28 days prior to the initial dose of trial medication, any medication known to induce or inhibit CYP3A4 enzyme activity that may have affected estrogen and/or progestin drug metabolism.
21. Had used, within 28 days prior to Screening, or planned to use during the trial, any prescription or over the counter (OTC) medication (including herbal products, such as St. John's Wort) that would be expected to alter progesterone or estrogen activity or is being used to treat vasomotor symptoms.
22. Had used estrogen alone or estrogen/progestin, selective estrogen receptor modulator (SERM), testosterone, or estrogen/testosterone for any of the following time periods:
    a) Vaginal non-systemic hormonal products (rings, creams, gels) within 7 days prior to Screening, or vaginal systemic products (for example, Femring®) within 28 days prior to Screening.
    b) Transdermal estrogen alone or estrogen/progestin products within 8 weeks prior to Screening,
    c) Oral estrogen and/or progestin therapy and/or SERM within 8 weeks prior to Screening,
    d) Progestational implants, estrogen or estrogen/progestational injectable drug therapy within 3 months prior to Screening,
    e) Estrogen pellet therapy or progestational injectable drug therapy within 6 months prior to Screening,
    f) Percutaneous estrogen lotions/gels within 8 weeks prior to Screening,
    g) Oral, topical, vaginal, patch, implantable or injectable androgen therapy within 8 weeks prior to Screening.
23. Had used an intrauterine device within the 12 weeks prior to Screening.
24. For participants in the VMS subtrial only: use of medication that may have affected the outcome of the VMS endpoints within 28 days prior to Screening (for example, selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], aldomet, dopaminergic or antidopaminergic drugs, gabapentin, clonidine, or bellergal).
25. Had any reason which, in the opinion of the investigator, would prevent the woman from safely participating in the trial or complying with protocol requirements.
26. Had a Screening endometrial biopsy sample that was found by both primary pathologists to have endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified (with the approval of the medical monitor, the Screening endometrial biopsy could have been repeated once).
27. Endometrial polyps with atypical nuclei reported by at least one central pathologist.

28. Had contraindication to any planned study assessments (for example, endometrial biopsy).
29. Had participated in another clinical trial within 30 days prior to Screening, had received an investigational drug within the three months prior to the initial dose of trial medication, or was likely to participate in a clinical trial or receive another investigational medication during the study.
30. Current use of marijuana.

Clinical Reviewer's Comments:
The exclusion criteria in Trial TXC12-05 were comprehensive and complete, and considered appropriate for this phase 3 clinical trial.

Individual Trial Participant Stopping Criteria:
Women were removed from the trial if any of the following circumstances occurred:

- The woman withdrew her consent for any reason.
- The woman's condition worsened to the degree that the investigator felt it was unsafe for the woman to continue in the trial.
- If it was difficult/impossible to obtain laboratory samples.
- If the woman's drug code was unblinded.
- If an AE occurred for which the woman desired to discontinue treatment or the investigator determined that it was in the woman's best interest to be discontinued.
- If there was a significant protocol deviation/violation or a trend in deviations/violations (defined as a deviation/violation that affects the woman's rights, safety, or the integrity of the trial data).
- If a concomitant therapy was reported or required which was likely to interfere with the results of the trial or compromise trial participant safety.
- If the woman was lost to follow-up. The investigator was to document efforts to attempt to reach the participant at least twice by telephone and by a certified follow-up letter before considering that the participant was lost to follow-up.
- If a woman became pregnant. If a pregnancy was reported during trial participation, the pregnancy was to be followed as medically appropriate.
- Administrative reasons.

If a woman was discontinued from the trial for any reason, every attempt was to be made to bring the woman to the clinic and perform the end-of-trial(EOT) procedures. Any outstanding data was captured and the trial medication, diaries and supplies were collected.

If a woman discontinued from the trial at any time due to an adverse event (AE), the reason for discontinuation, the nature of the event and its clinical course were fully documented. The investigator followed the woman until the AE resolved, became clinically insignificant, or was

stabilized, unless the woman was lost to follow-up. If a woman discontinued or withdrew, she was not replaced.

Primary Efficacy Endpoints (VMS Subtrial):

The following co-primary efficacy endpoints were assessed in the VMS subtrial:

- Mean change in frequency of moderate to severe VMS from Baseline to Week 4 in an active treatment group compared with placebo
- Mean change in frequency of moderate to severe VMS from Baseline to Week 12 in an active treatment group compared with placebo
- Mean change in severity of moderate to severe VMS from Baseline to Week 4 in an active treatment group compared with placebo
- Mean change in severity of moderate to severe VMS from Baseline to Week 12 in an active treatment group compared with placebo

Clinical Reviewer's Comments:

The primary efficacy endpoints in the Trial TXC12-05 VMS subtrial are appropriate, and comply with the Agency's 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy symptoms – Recommendations for Clinical Evaluation (hereafter referred to as the Agency's draft 2003 Hormone Therapy Guidance for Industry).[7]

Secondary Endpoints from the VMS Subtrial:

- Mean change in frequency of moderate to severe VMS from Baseline to each week up to Week 12 in an active treatment group compared with placebo.
- Mean change in severity of moderate to severe VMS from Baseline to each week up to Week 12 in an active treatment group compared with placebo.
- Mean change in frequency of mild, moderate and severe VMS from Baseline to each week up to Week 12 in an active treatment group compared with placebo.
- Mean change in severity of mild, moderate and severe VMS from Baseline to each week up to Week 12 in an active treatment group compared with placebo.
- Percentage of participants with 50% and, separately, 75% reduction in frequency of moderate to severe VMS from Baseline at each week up to Week 12 in an active treatment group compared with placebo.
- Percentage of participants with 50% and, separately, 75% reduction in frequency of mild, moderate and severe VMS from Baseline at each week up to Week 12 in an active treatment group compared with placebo.

[7] The Agency's 2003 draft hormone therapy clinical evaluation Guidance for Industry can be viewed at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133343.pd

- Clinical Global Impression (CGI) distribution (number and percentage of participants in VMS substudy only) at Week 4, Week 8, and Week 12, with mean change in the frequency of moderate to severe VMS from Baseline summarized within each CGI category at Weeks 4, 8, and 12 (Gerlinger method). This was utilized to evaluate minimum clinically important changes in VMS frequency that are associated with each CGI category.
- Change from Baseline in Menopause-Specific Quality of Life (MENQOL) evaluation parameter,
- Change from Baseline in Medical Outcome Study - Sleep (MOS – Sleep) evaluation parameters.

Other Secondary Efficacy Endpoints (Modified Intent-to-Treat):
Other secondary efficacy endpoints include:

- Change from Baseline in MENQOL evaluation parameters
- Change from Baseline in MOS - Sleep evaluation parameters

Clinical Reviewer's Comments:
On November 7, 2013, in an Advice/Information Request (A/IR) letter, TherapeuticsMD was advised that:

- only data collected on the primary endpoint will be presented in product labeling. Data collected for the proposed secondary endpoints in the vasomotor symptoms (VMS) subtrial will not be used to determine the effectiveness of the drug product for the indications sought, nor will this data appear in product labeling, and
- the findings from secondary endpoints and other endpoints (for example, MENQOL evaluation parameters and MOS-Sleep evaluation parameters) would not be used to support the effectiveness of the drug product to relieve hot flushes and would not appear in labeling.

Primary Safety Endpoints:
The primary safety endpoint is the incidence of endometrial hyperplasia at 12 months (to demonstrate a hyperplasia proportion that was ≤ 1% with an upper bound of the one-sided 95 percent confidence interval [CI] for that rate that does not exceed 4%) based on an *a priori* plan which a consensus among two out of three pathologists was the final endometrial pathology diagnosis.

For the primary endpoint, all endometrial biopsies were centrally read by three pathologists. Each pathologist classified the endometrial biopsies into one of the following three categories:

- Category 1: Non-endometrial malignancy/non-hyperplasia includes proliferative endometrium, weakly proliferative endometrium, disordered proliferative pattern, secretory endometrium, endometrial tissue (other) [benign, inactive or atrophic

fragments of endometrial epithelium, glands, stroma, etc], endometrial tissue insufficient for diagnosis, no endometrium identified, no tissue identified, other.

- Category 2: Endometrial hyperplasia includes simple hyperplasia with or without atypia and complex hyperplasia with or without atypia.
- Category 3: Endometrial malignancy.

Clinical Reviewer's Comments:

The Agency's draft 2003 hormone therapy Guidance for Industry recommends that standardized criteria, as provided in Blaustein's pathology text (Pathology of the Female Genital Tract), be used for the diagnosis of endometrial hyperplasia or cancer.[7] Standardized Histologic Characteristics of the Endometrium under Blaustein's Pathology of the Female Genital Tract is divided into the following individual histologic characteristics:

0. No tissue
1. Tissue insufficient for diagnosis
2. Atrophic
3. Inactive
4. Proliferative
    a. Weakly proliferative
    b. Active proliferative
    c. Disordered proliferative
5. Secretory
    a. Cystic type
    b. Progestational type
6. Menstrual type
7. Simple hyperplasia without atypia
8. Simple hyperplasia with atypia
9. Complex hyperplasia without atypia
10. Complex hyperplasia with atypia
11. Carcinoma (specify type)

No grouping of the 11 individual histologic characteristics is recommended.

Secondary Safety Endpoints:

Endometrial biopsies were performed at Screening and at Visit 7 (Month 12)/End-of-Trial by a board-certified gynecologist and the procedure, including instrument used, was documented in the trial participant's source file. Trial participants who discontinued trial participation after receiving ≥ 12 weeks of trial medication were also required to have an endometrial biopsy. Unscheduled endometrial biopsies were performed during the trial, if indicated for medical reasons.

Biopsy specimens were shipped to a central laboratory ([redacted] (b) (4) for preparation of slides. To ensure uniformity in interpretation, a chartered Pathology Committee consisting of four independent pathologists (one pathologist was a back-up in the event of illness or unavailability of the other pathologists), who are experts in the field of endometrial pathology, assessed the endometrial biopsy samples in a blinded fashion.

At Screening, endometrial biopsies were read centrally by two pathologists. If at least one pathologist assessed the endometrial biopsy as endometrial hyperplasia, endometrial cancer, or if either pathologist identifies an endometrial polyp with either hyperplasia, glandular atypia of any degree (for example, atypical nuclei) or cancer, the woman was excluded from the trial. Additionally, at least one pathologist had to identify sufficient tissue to evaluate the biopsy for trial eligibility.

With the approval of the medical monitor, the Screening endometrial biopsy may have been repeated once when an initial endometrial biopsy was performed and both primary pathologists reported endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified, and if the woman had met all other protocol-specified eligibility criteria to date.

The Month 12/ End-of-Trial, Early Termination, and on-treatment unscheduled biopsies were centrally read by three pathologists. The End-of-Trial or Early Termination biopsy may have been repeated once if all three of the pathologists reported endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified. End-of-Trial or Early Discontinuation endometrial biopsies that were repeated per protocol must have been performed within 30 days of the final dose of trial medication.

Per the application, the reads of the two primary pathologists were utilized. Consensus was reached when the two primary pathologist readers agreed on any of the above categories. For example, any two subcategories of “Non-endometrial malignancy/non-hyperplasia” were classified as “Category 1: Non-endometrial malignancy/non-hyperplasia”; if the primary pathologists disagreed on the presence of hyperplasia, the result of the third pathologist was utilized and the final decision regarding the presence of hyperplasia was based on the diagnosis of the majority. If all three readings were disparate (each fell into a different category – Category 1, 2, or 3), the final diagnosis was based on the most severe of the three readings. A secondary analysis was performed utilizing the three pathologist reads as described in Section 9.5.4.2.1. If a woman was diagnosed with endometrial hyperplasia at any time during the trial, they were given appropriate treatment (progestogen) at the discretion of the investigator and every attempt to follow-up to resolution was made.

For unscheduled biopsies, the histological diagnosis of endometrial polyp did not require withdrawal, unless hyperplasia or atypical nuclei were present.

Per the application, a supplemental secondary analysis was performed based on the results from the three pathologists. In this supplemental analysis, the final diagnosis was based on agreement of two of the three pathologists reads. Consensus was reached when two of the three pathologist readers agreed on any of the above categories. For example, any two subcategories of "Non-endometrial malignancy/non-hyperplasia" was classified as "Category 1: Non-endometrial malignancy/non-hyperplasia." If all three readings were disparate (each fell into a different category – Category 1, 2, or 3), the final diagnosis was based on the most severe of the three readings.

> Clinical Reviewer's Comments:
> This reviewer considers the endometrial biopsy specimen diagnosis of three individual, independent pathologists to be the primary analysis, and not a supplemental secondary analysis. The 2003 draft Hormone Therapy Guidance for Industry recommends concurrent readings by three independent expert pathologists from institutions with independent fiduciary and organizational reporting. Each pathologist should be blinded to the treatment group and to the readings of the other pathologists. The concurrence of two of the three pathologists is accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis would be used as the final diagnosis.
>
> See Subsection 8.5.1 of this review for a more detailed discussion of the reported endometrial safety findings.

Other Secondary Endpoints (All Participants):
Other secondary endpoints included:

- Proportion of women with cumulative amenorrhea from Day 1 to Day 364
- No bleeding: percent by cycle and cumulative for consecutive 28-day cycles
- Number of days with bleeding/spotting

Additional Safety Endpoints:
Overall safety variables included:

- Trial participant incidence of AEs and serious adverse events (SAEs)
- Trial participant incidence of endometrial polyps
- Change from Baseline in:
  - Clinical laboratory testing (hematology, clinical chemistry, coagulation and urinalysis [where applicable])
  - Vital signs
  - Physical examination findings
  - Body weight and BMI

- Gynecological Examination (pelvic examination, Pap smear, and breast examination)
- Mammogram (BI-RADS)
- 12-lead ECG
- Hormone concentration levels for serum estradiol, estrone, and progesterone

Statistical Analysis Plan (SAP):
Statistical analysis and programming of tables and listings was conducted by a designee of the sponsor, using SAS® Release 9.2 or higher (SAS Institute Inc, Cary, North Carolina, USA). The statistical analysis plan, version 1 for Trial TXC12-05, was submitted September 21, 2016; version 2 for Trial TXC12-05, was submitted November 15, 2016.

The overall Trial TXC12-05 sample size was based on the target that the combination therapy was effective at achieving a ≤ 1% incidence rate of endometrial hyperplasia following 12-months of therapy, and that the upper bound of the 95% confidence interval of the estimated incidence rate was ≤ 4%. The VMS subtrial sample size was based on the expected changes in average weekly frequency and severity of VMS from Baseline to Weeks 4 and 12.

The sample size for the VMS endpoint was based on the change in frequency and severity of hot flashes between the active treatment groups and placebo. All attempts were made to prevent any missing values. Each of the four active treatment groups and the four co-primary outcomes was compared to the placebo group in a hierarchical order to preserve the test level of significance for each comparison at 5% (two-sided). A Mixed Effect Model Repeat Measurement (MMRM) model was used for the final analysis, and a two-group t-test was used to estimate sample size requirements for the VMS subtrial.

Datasets Analyzed:

- Safety Population - All women who were randomly assigned and had taken at least one capsule of trial medication formed the Safety population. Analysis was based on the actual treatment the women took on trial Day 1. Trial participants who were found to have participated in the trial twice with two separate randomization numbers were included in the AEs and endometrial safety summaries only.
- Endometrial Safety (ES) Population - The analysis population for endometrial safety is the ES population. An ES trial participant is all randomized trial participants who:
  - had taken at least one capsule of trial medication as documented (analysis was based on the actual treatment the trial participant took on trial Day 1);
  - had no major protocol violations (the medical monitor made the final decision on exclusion and the list was provided prior to unblinding);
  - had an acceptable biopsy at Baseline (at least one endometrial biopsy with evaluable tissue and no read of endometrial hyperplasia or cancer, or

endometrial polyp with either hyperplasia, glandular atypia of any degree (for example, atypical nuclei) or cancer; and

- had an endometrial biopsy at Month 12 (defined as on or after trial Day 326) or had a diagnosis of endometrial hyperplasia prior to Month 12.

Participating women who had an endometrial malignancy were not included in the numerator or denominator of the incidence calculation, per the SAP. Participating women who were found to have participated in the trial twice with two separate randomization numbers were included in the AEs and endometrial safety summaries only.

The incidence rate of endometrial hyperplasia at Month 12 was calculated as follows:

I = A / B

Where I = incidence rate at Month 12 evaluation
A = all new participants with biopsies positive for endometrial hyperplasia during the study, but post-Baseline
B = all participants with biopsies following Month 11 meeting the criteria specified above, plus all participants with biopsies positive for endometrial hyperplasia by any of the pathologist before Month 11

An upper one-sided 95% confidence limit for the binomial proportion was calculated. In addition, 95% two-sided CIs were calculated for pairwise differences between groups in hyperplasia incidence.

- Modified Intent-to-Treat (MITT) Population - The overall MITT population was comprised of all randomized women who took at least one dose (two capsules, one active and one placebo) of trial medication. Analysis was based on the treatment group to which the woman was randomized. Trial participants who were found to have participated in the trial twice with two separate randomization numbers were excluded.
- MITT- VMS Population - The MITT – VMS population was the primary efficacy population. To be included in the MITT-VMS population, women must have been randomized to the VMS subtrial, had taken at least one dose (two capsules, one active and one placebo) of trial medication, and:
    1) had at least five (5) days of VMS diary data for Baseline measurement of frequency and severity of moderate to severe hot flushes; and
    2) had at least four (4) days of VMS diary data for one on-treatment week of reporting of frequency and severity of hot flushes following initiation of trial medication.

Analysis was based on the treatment group to which the woman was randomized.

- Efficacy Evaluable (EE) – VMS - Trial participants were included in the EE-VMS population if they were randomized to the VMS subtrial, had taken at least one dose (two capsules, one active and one placebo) of trial medication, and:
    1) had at least seven per day or 50 per week moderate to severe hot flashes at Baseline;
    2) had no major protocol violations that could impact the VMS endpoint (the medical monitor made the final decision on exclusion and the list was provided by the sponsor prior to unblinding);
    3) had at least four (4) days of VMS diary data for one on-treatment week of reporting of frequency and severity of hot flashes following initiation of trial medication; and
    4) had no dispensing error (defined as a participant who initiated the trial with one treatment group but during the first 12-weeks of treatment inadvertently received an incorrect wallet from another randomization code).
- Bleeding Population - Trial participants who took at least one dose (two capsules, one active and one placebo) of trial medication and who had at least one post- Baseline bleeding/spotting diary entry comprised the bleeding population. Women evaluated included the safety population less any women who had no bleeding/spotting diary data. Bleeding data collected for the day on which an endometrial biopsy was performed, and for the six (6) days thereafter, was excluded for both cumulative and non-cumulative summaries. The last available data before the biopsy was performed was carried forward for those days (LOCF). The number of days with bleeding/spotting, as reported on subject diaries, was summarized by cycle and treatment group.

  No bleeding was defined as absence of bleeding. Within each treatment group, the percent of women with no bleeding was calculated by cycle and for consecutive cycles and compared between active and placebo treatments.

  Cumulative rates for no bleeding was defined as the percentage of women who reported consecutive cycles of no bleeding for a given cycle of time. For example, if a woman had no bleeding from Day 1 to Day 364, then this woman had no bleeding from the 1st to 13th cycle. The number and percentage of woman with no bleeding for each cumulative period was summarized separately for the 1st to 13th cycle, 2nd to 13th cycle, …, and the 13th cycle.

Efficacy Analysis:
All efficacy analyses were performed on the MITT-VMS and EE-VMS populations. The primary population was the MITT-VMS population and the secondary population for all efficacy analyses was the more restrictive EE-VMS population.

Four pair-wise comparisons were performed for Week 4 and Week 12 (co-primary) changes

from Baseline:

- Combined 1 mg estradiol/100 mg progesterone formulation versus placebo
- Combined 0.5 mg estradiol/100 mg progesterone formulation versus placebo
- Combined 0.5 mg estradiol/50 mg progesterone formulation versus placebo
- Combined 0.25 mg estradiol/50 mg progesterone formulation versus placebo

Within each dose level/placebo comparison, there were four co-primary efficacy endpoints. The four co-primary endpoints were each tested at level alpha (0.05, two-tailed).

Within each active dose/placebo comparison, there were four co-primary endpoints:

- Mean change in frequency of moderate to severe VMS from Baseline to Week 4
- Mean change in frequency of moderate to severe VMS from Baseline to Week 12
- Mean change in severity of moderate to severe VMS from Baseline to Week 4
- Mean change in severity of moderate to severe VMS from Baseline to Week 12.

A gatekeeping (hierarchal) testing procedure was followed to account for the multiple comparisons of testing placebo to each of the four active doses of TX-001HR and the multiple testing of the four co-primary endpoints. The testing started by examining the highest dose (combined 1 mg estradiol plus 100 mg progesterone) for the co-primary endpoints. If the four p-values for the co-primaries were significant ($p \leq 0.05$) then the hypothesis testing continued to the next dose (combined 0.5 mg estradiol plus 100 mg progesterone) for each of the co-primary endpoints, as described above. If at any point the hypothesis testing yielded a non-significant result, the testing was stopped. The gatekeeping procedure described was also followed for all secondary efficacy endpoint comparisons of each active treatment group with placebo.

The weekly number of moderate to severe hot flushes for each assessment week (Baseline, and Weeks 1 through Week 12) was derived as:

- Weekly Frequency = total number of moderate and severe hot flushes for the participant's week.

The weekly severity of hot flushes for the change in severity of moderate to severe vasomotor symptoms was derived as:

- Baseline Weekly Severity Score = (number of moderate hot flushes for 7 days) x 2 + (number of severe hot flushes for 7 days) x 3/total number of moderate to severe hot flushes over 7 days.
- On Treatment Weekly Severity Score = (number of mild hot flushes for 7 days) x 1 + (number of moderate hot flushes for 7 days) x 2 + (number of severe hot flushes for 7 days) x 3/total number of mild, moderate and severe hot flushes over 7 days).

The weekly frequency of mild, moderate and severe hot flushes was calculated using the same method as for moderate to severe hot flushes but with the number of mild hot flushes added to the sum. Weekly severity of hot flushes for the change in severity of mild, moderate to severe VMS was derived in the same way as above except in the Baseline calculation, mild hot flushes were included. A weekly severity score of zero (0) was assigned for participants reporting no hot flushes for a given assessment week.

Absolute changes from baseline and respective differences from placebo in frequency and severity of VMS was listed and summarized. Means, SDs, minimum (MIN) and maximum (MAX) are provided for the co-primary efficacy endpoints. A mixed model repeated measure (MMRM) analysis was applied to the 12 weekly change scores. The model included Baseline as covariate, treatment, trial week, and treatment-by-trial week interaction as fixed factors, and participant as the repeated measure unit. Trial week pertained to the 12-individual weekly hot flushes frequency derivations. The variance-covariance matrix of the change scores over time was assumed to be unstructured. If the computation did not converge, the covariance structure was reduced from, in the order of, "unstructured (UN)", "Toeplity (TOEP)", "autoregressive order 1 [AR(1)]" to "compound symmetry (CS)". Ninety-five percent (95%), two-sided CIs were derived for least square (LS) mean changes from Baseline and respective differences from placebo for each dose and week. The gatekeeping procedure for the primary efficacy endpoints already described was used in the interpretation of P-values and the confidence intervals.

In addition to the principal MMRM analysis of the four co-primary endpoints, a sensitivity evaluation was also conducted using an analysis of covariance (ANCOVA); SAS generalized linear model utilizing last observation carried forward (LOCF). For women who discontinued the trial prior to Week 12 or who had missing data at Weeks 4 or 12, the last observed weekly hot flush frequency or severity value was carried forward to all visits through Week 12. Women who had no post-Baseline data were not included in the ANCOVA consideration (that is, there was no baseline observation carried forward application). The sensitivity evaluation was specifically designed to provide support for the MMRM; the primary MMRM approach was considered to have the most power for statistical inferences and was the principal *a priori* analysis method.

Analysis of Secondary Efficacy - Frequency and Severity of VMS:
Similar to the continuous co-primary endpoints for Weeks 4 and 12, the same MMRM model was applied to the changes in frequency and severity of mild, moderate and severe vasomotor symptoms for each assessment week up to Week 12. The calculation for frequency and severity of hot flushes remained the same, with the exception that hot flushes of all severities was included.

Responder Analysis:
Responders were defined as the percent of women with 50% and, separately, 75% reduction

from Baseline in moderate to severe VMS at Week 12 compared between active and placebo treatments. These proportions were calculated and presented graphically. Simple comparisons of proportions using the Fisher's exact test were made for each active treatment group compared to placebo. The gatekeeping approach for the primary efficacy endpoints previously described was employed for the formulation of inferences concerning each comparison.

Analysis of Secondary Efficacy:

- CGI: The number and percentage of women for each category of the CGI was summarized at Week 4, Week 8, and Week 12, with mean change in the frequency of moderate to severe VMS from Baseline summarized within each CGI category at Weeks 4, 8, and 12. Trial participants were asked to answer the question "Rate the total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to your condition at administration to the study, how much has it changed using the following scale:
    - Very much improved
    - Much improved
    - Minimally improved
    - No change
    - Minimally worse
    - Much worse
    - Very much worse"

  Descriptive analyses were conducted to show the mean changes in frequency of moderate to severe VMS at 12 weeks by different categories of change based on the CGI. The analysis focused on Baseline to Week 12 changes for estimating minimal important differences and responder groups. The minimal important difference was defined based on CGI ratings of 'minimally improved' category, and clinically meaningful responders were defined based on CGI ratings of 'much improved' or 'very much improved' combined. The worsen/no change group was defined as consisting of those women reporting CGI ratings of 'no change' to 'very much worse'. Based on these CGI response groupings, a three-categorical variable was constructed and a nonparametric discriminate analysis was conducted utilizing bootstrapping methods.
- MENQOL: The MENQOL questionnaire assessed changes in quality of life of study subjects over a one-month period. It was self-administered and was measured at Baseline, Week 12, Month 6 and Month 12 during the trial. It is composed of 29 questions distributed across four domains: vasomotor, psychosocial, physical and sexual. Change from Baseline in monthly scores were summarized and described within each treatment group for the MITT-VMS population and the MITT population.
- MOS – Sleep: The MOS - Sleep self-report questionnaire is composed of 12 items that measure six dimensions of sleep over the past four weeks. It was self-administered and was measured at Baseline, Week 12, Month 6, and Month 12 during the trial. Change in

scores over the past four weeks (total and subscales) were summarized within each treatment group for the MITT-VMS population and MITT populations separately. Most questions were scored with one of six numbers ranging from 1 (all of the time) to 6 (none of the time), indicating the frequency of various aspects of the disease-related sleep disruption over the preceding week. Women also estimated the average amount of sleep per night during the past week.

Proportion of Subjects in the Safety Population with Cumulative Amenorrhea from Day 1 to Day 364:

Amenorrhea was defined as absence of bleeding or spotting. Within each treatment arm, the portion of women with cumulative amenorrhea from Day 1 to Day 364 was calculated and compared between active and placebo treatments. Cumulative rates of amenorrhea were defined as the percentage of women who reported consecutive cycles of amenorrhea for a given cycle of time. For example, if a woman had no bleeding or spotting from Day 1 to Day 364, then this woman had cumulative amenorrhea from the 1st to 13th cycle. The number and percentage of women with amenorrhea for each cumulative period was summarized separately for the 1st to 13th cycle, 2nd cycle to 13th cycle, …, and the 13th cycle.

Protocol Amendments for Trial TXC12-05:

The original protocol (Version 1.0) was approved on February 18, 2013. Overall, five (5) protocol amendments were submitted (Amendment # 1 dated May 15, 2013, Amendment # 2 dated June 24, 2013, Amendment # 3 dated August 15, 2013, Amendment # 4 dated February 18, 2014, and Amendment # 5 dated June 3, 2014). The Clinical Study Report for Trial TXC12-05 included in the NDA application encompasses Protocol Amendment # 6.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Debarment Certification, dated November 15, 2017, signed by Christine Miller, PharmD, Chief Regulatory and Quality Officer, states "TherapeuticsMD, Inc hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."

Data management responsibilities and all data were transferred from (b) (4) to (b) (4) in 2014. The data entry system (eCRF) was then managed by (b) (4) based on specifications from TherapeuticsMD. (b) (4) data management platform, (b) (4), was used to integrate the electronic data capture (EDC), data management (DM), Safety reporting, Interactive Web Response System (IWRS), and IP management. TherapeuticsMD, in conjunction with (b) (4) was responsible for coding the concomitant medications using the World Health Organization Drug Dictionary (WHODD) term per the

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PREMPRO/PREMPHASE safely and effectively. See full prescribing information for PREMPRO/PREMPHASE.

PREMPRO® (conjugated estrogens/medroxyprogesterone acetate tablets) PREMPHASE® (conjugated estrogens plus medroxyprogesterone acetate tablets)
Initial U.S. Approval: 1995

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER, ENDOMETRIAL CANCER and PROBABLE DEMENTIA
See full prescribing information for complete boxed warning.

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI) (5.1)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)**
- **The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The WHI estrogen-alone substudy reported increased risks of stroke and DVT (5.1)**
- **The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

---------- RECENT MAJOR CHANGES ----------
Warnings and Precautions, Malignant Neoplasms (5.2) 11/2017

———— INDICATIONS AND USAGE ————
PREMPRO/PREMPHASE is an estrogen plus progestin indicated in a woman with a uterus for:

- Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause (1.1)
- Treatment of Moderate to Severe Vulvar and Vaginal Atrophy due to Menopause (1.2)
- Prevention of Postmenopausal Osteoporosis (1.3)

———— DOSAGE AND ADMINISTRATION ————
PREMPRO: one tablet containing conjugated estrogens (CE) plus medroxyprogesterone acetate (MPA) taken orally once daily. (2)

PREMPHASE: one maroon tablet containing 0.625 mg CE taken orally on days 1 through 14, and one light-blue tablet containing 0.625 mg CE plus 5.0 mg MPA taken orally on days 15 through 28. (2)

———— DOSAGE FORMS AND STRENGTHS ————
PREMPRO Tablets: 0.3 mg CE plus 1.5 mg MPA, 0.45 mg CE plus 1.5 mg MPA, 0.625 mg CE plus 2.5 mg MPA, 0.625 mg CE plus 5 mg MPA.

PREMPHASE Tablets: 0.625 mg CE, 0.625 mg CE plus 5 mg MPA.

———— CONTRAINDICATIONS ————

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.2)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema to PREMPRO/PREMPHASE (5.15, 5.16)
- Known liver dysfunction or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

———— WARNINGS AND PRECAUTIONS ————

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid replacement therapy (5.11, 5.19)

———— ADVERSE REACTIONS ————
In two prospective, randomized clinical studies, the most common adverse reactions > 5 percent are abdominal pain, asthenia, back pain, headache, flatulence, nausea, depression, pruritus, breast pain, dysmenorrhea, and leukorrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

———— DRUG INTERACTIONS ————

- Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)
- Aminoglutethimide administered concomitantly with MPA may significantly depress the bioavailability of medroxyprogesterone acetate (7.1)

———— USE IN SPECIFIC POPULATIONS ————

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (5.3, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS *

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER, ENDOMETRIAL CANCER and PROBABLE DEMENTIA

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.6, 14.7)]*.

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported an increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogen (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.6)]*.

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2), and Clinical Studies (14.6)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when

indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.2)]*.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.6, 14.7)]*.

The WHI estrogen-alone substudy reported increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral CE (0.625 mg)-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.6)]*.

The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

1.2 Treatment of Moderate to Severe Vulvar and Vaginal Atrophy due to Menopause

1.3 Prevention of Postmenopausal Osteoporosis

2 DOSAGE AND ADMINISTRATION

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

PREMPRO therapy consists of a single tablet to be taken orally once daily.

PREMPHASE therapy consists of two separate tablets: one maroon 0.625 mg Premarin [conjugated estrogens (CE)] tablet taken daily on days 1 through 14 and one light-blue tablet containing 0.625 mg CE and 5 mg of medroxyprogesterone acetate (MPA) taken on days 15 through 28.

2.2 Treatment of Moderate to Severe Vulvar and Vaginal Atrophy due to Menopause

PREMPRO therapy consists of a single tablet to be taken orally once daily.

PREMPHASE therapy consists of two separate tablets: one maroon 0.625 mg CE tablet taken daily on days 1 through 14 and one light-blue tablet containing 0.625 mg CE and 5 mg MPA taken on days 15 through 28.

When prescribing solely for the treatment of moderate to severe vulvar and vaginal atrophy, topical vaginal products should be considered.

2.3 Prevention of Postmenopausal Osteoporosis

PREMPRO therapy consists of a single tablet to be taken orally once daily.

PREMPHASE therapy consists of two separate tablets: one maroon 0.625 mg CE tablet taken daily on days 1 through 14 and one light-blue tablet containing 0.625 mg CE and 5 mg of MPA taken on days 15 through 28.

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

3 DOSAGE FORMS AND STRENGTHS

PREMPRO (conjugated estrogens/medroxyprogesterone acetate tablets)		
Tablet Strength	Tablet Shape/Color	Imprint
0.3 mg CE plus 1.5 mg MPA	oval / cream	PREMPRO 0.3/1.5
0.45 mg CE plus 1.5 mg MPA	oval / gold	PREMPRO 0.45/1.5
0.625 mg CE plus 2.5 mg MPA	oval / peach	PREMPRO 0.625/2.5
0.625 mg CE plus 5 mg MPA	oval / light blue	PREMPRO 0.625/5

PREMPHASE (conjugated estrogens/medroxyprogesterone acetate tablets)		
Tablet Strength	Tablet Shape/Color	Imprint
0.625 mg CE	oval / maroon (14 tablets)	PREMARIN 0.625
0.625 mg CE plus 5 mg MPA	oval / light-blue (14 tablets)	PREMPRO 0.625/5

4 CONTRAINDICATIONS

PREMPRO or PREMPHASE therapy should not be used in women with any of the following conditions:

- **Undiagnosed abnormal genital bleeding**
- **Known, suspected, or history of breast cancer**
- **Known or suspected estrogen-dependent neoplasia**
- **Active DVT, PE, or a history of these conditions**
- **Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions**
- **Known anaphylactic reaction or angioedema to PREMPRO/PREMPHASE**
- **Known liver dysfunction or disease**
- **Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders**
- **Known or suspected pregnancy**

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. An increased risk of stroke and DVT has been reported with estrogen-alone therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.6)]*. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.6)]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.6)]*.

In the WHI estrogen-alone substudy, no overall effect on CHD events was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.6)]*.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[3] *[see Clinical Studies (14.6)]*. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, the risk of VTE was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[4] *[see Clinical Studies (14.6)]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

5.2 Malignant Neoplasms

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years, for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[5] *[see Clinical Studies (14.6)]*.

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg)-alone was not

associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*[6] *[see Clinical Studies (14.6)]*.

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Endometrial Cancer

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with PREMPRO or PREMPHASE.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for

CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7]

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

5.3 Probable Dementia

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.7)]*.

5.4 Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5.5 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

5.7 Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

5.8 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

5.9 Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5.11 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their

thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

5.12 Fluid Retention

Estrogens plus progestins may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens plus progestins are prescribed.

5.13 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.14 Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

5.15 Anaphylactic Reaction and Angioedema

Cases of anaphylaxis, which developed within minutes to hours after taking PREMPRO or PREMPHASE and require emergency medical management, have been reported in the postmarketing setting. Skin (hives, pruritis, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) involvement has been noted.

Angioedema involving the tongue, larynx, face, hands, and feet requiring medical intervention has occurred postmarketing in patients taking PREMPRO or PREMPHASE. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop an anaphylactic reaction with or without angioedema after treatment with PREMPRO or PREMPHASE should not receive PREMPRO or PREMPHASE again.

5.16 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

5.17 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

5.18 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

5.19 Drug-Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay), or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Malignant Neoplasms *[see Boxed Warning, Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 1-year clinical trial that included 678 postmenopausal women treated with PREMPRO and 351 postmenopausal women treated with PREMPHASE, the following adverse reactions occurred at a rate ≥ 1 percent, see Table 1.

TABLE 1: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625 mg/2.5 mg continuous (n = 340)	PREMPRO 0.625 mg/5 mg continuous (n = 338)	PREMPHASE 0.625 mg/5 mg sequential (n = 351)
Body As A Whole			
Abdominal pain	35 (10%)	51 (15%)	58 (17%)
Asthenia	13 (4%)	18 (5%)	21 (6%)
Back pain	19 (6%)	16 (5%)	23 (7%)
Chest pain	5 (1%)	4 (1%)	4 (1%)
Flu syndrome	1 (<1%)	1 (<1%)	4 (1%)
Generalized edema	12 (4%)	12 (4%)	8 (2%)
Headache	64 (19%)	52 (15%)	66 (19%)
Infection	2 (<1%)	4 (1)%	0
Moniliasis	4 (1%)	3 (<1%)	4 (1%)
Pain	12 (4%)	14 (4%)	15 (4%)
Pelvic pain	11 (3%)	13 (4%)	16 (5%)
Cardiovascular System			
Hypertension	7 (2%)	7 (2%)	6 (2%)
Migraine	6 (2%)	8 (2%)	7 (2%)
Palpitation	2 (<1%)	3 (<1%)	4 (1%)
Vasodilatation	2 (<1%)	7 (2%)	2 (<1%)
Digestive System			
Diarrhea	4 (1%)	3 (<1%)	7 (2%)
Dyspepsia	5 (1%)	5 (1%)	7 (2%)
Eructation	0	2 (<1%)	4 (1%)
Flatulence	25 (7%)	27 (8%)	24 (7%)
Increased appetite	1 (<1%)	5 (1%)	5 (1%)
Nausea	26 (8%)	19 (6%)	26 (7%)
Metabolic and Nutritional			
Edema	5 (1%)	6 (2%)	3 (<1%)
Glucose tolerance decreased	2 (<1%)	5 (1%)	4 (1%)
Peripheral edema	11 (3%)	10 (3%)	11 (3%)
Weight gain	9 (3%)	10 (3%)	11 (3%)

TABLE 1: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625 mg/2.5 mg continuous (n = 340)	PREMPRO 0.625 mg/5 mg continuous (n = 338)	PREMPHASE 0.625 mg/5 mg sequential (n = 351)
Musculoskeletal System			
Arthralgia	6 (2%)	2 (<1%)	7 (2%)
Leg cramps	8 (2%)	11 (3%)	12 (3%)
Nervous System			
Depression	14 (4%)	26 (8%)	29 (8%)
Dizziness	9 (3%)	8 (2%)	7 (2%)
Emotional lability	5 (1%)	5 (1%)	6 (2%)
Hypertonia	4 (1%)	4 (1%)	7 (2%)
Insomnia	7 (2%)	6 (2%)	4 (1%)
Nervousness	4 (1%)	9 (3%)	6 (2%)
Skin and Appendages			
Acne	1 (<1%)	5 (1%)	4 (1%)
Alopecia	3 (<1%)	4 (1%)	0
Dry skin	2 (<1%)	3 (<1%)	4 (1%)
Pruritus	20 (6%)	18 (5%)	13 (4%)
Rash	8 (2%)	6 (2%)	7 (2%)
Sweating	2 (<1%)	4 (1%)	2 (<1%)
Urogenital System			
Breast engorgement	5 (1%)	5 (1%)	0
Breast enlargement	14 (4%)	14 (4%)	14 (4%)
Breast neoplasm	2 (<1%)	2 (<1%)	4 (1%)
Breast pain	110 (32%)	123 (36%)	109 (31%)
Cervix disorder	10 (3%)	6 (2%)	10 (3%)
Dysmenorrhea	26 (8%)	18 (5%)	44 (13%)
Leukorrhea	19 (6%)	13 (4%)	29 (8%)
Menstrual disorder	7 (2%)	1 (<1%)	5 (1%)
Menorrhagia	0	1 (<1%)	5 (1%)
Metrorrhagia	13 (4%)	5 (1%)	7 (1%)
Papanicolaou smear suspicious	5 (1%)	0	8 (2%)
Urinary incontinence	4 (1%)	2 (<1%)	1 (<1%)
Uterine spasm	7 (2%)	4 (1%)	7 (2%)
Vaginal hemorrhage	5 (1%)	3 (<1%)	8 (2%)
Vaginal moniliasis	5 (1%)	6 (2%)	7 (2%)

TABLE 1: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625 mg/2.5 mg continuous (n = 340)	PREMPRO 0.625 mg/5 mg continuous (n = 338)	PREMPHASE 0.625 mg/5 mg sequential (n = 351)
Vaginitis	13 (4%)	13 (4%)	10 (3%)

In addition, phargyngitis and sinusitis were reported as two of the more frequent adverse events (>5 percent) in the PREMPRO clinical study. For pharyngitis, of the 121 events, six events were considered by the investigator causally related to study drug. For sinusitis, of the 73 events, one event was considered as casually related to study drug.

During the first year of a 2-year clinical trial with postmenopausal women between 40 and 65 years of age (88 percent Caucasian), 989 postmenopausal women received continuous regimens of PREMPRO, and 332 received placebo tablets. Table 2 summarizes adverse reactions that occurred at a rate ≥ 1 percent in at least 1 treatment group.

TABLE 2: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY OF ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625/2.5 continuous (N=331)	PREMPRO 0.45/1.5 continuous (N=331)	PREMPRO 0.3/1.5 continuous (N=327)	PLACEBO daily (N=332)
Any adverse event	214 (65)	208 (63)	188 (57)	164 (49)
Body as a Whole				
Abdominal pain	38 (11)	33 (10)	24 (7)	21 (6)
Asthenia	11 (3)	11 (3)	12 (4)	3 (1)
Back pain	12 (4)	12 (4)	8 (2)	4 (1)
Chest pain	4 (1)	2 (1)	1 (0)	2 (1)
Generalized edema	7 (2)	5 (2)	6 (2)	8 (2)
Headache	45 (14)	45 (14)	57 (17)	46 (14)
Moniliasis	3 (1)	6 (2)	4 (1)	1 (0)
Pain	9 (3)	10 (3)	17 (5)	14 (4)
Pelvic pain	9 (3)	7 (2)	5 (2)	4 (1)
Cardiovascular System				
Hypertension	2 (1)	3 (1)	1 (0)	5 (2)
Migraine	11 (3)	8 (2)	5 (2)	3 (1)
Palpitation	1 (0)	1 (0)	2 (1)	4 (1)
Vasodilatation	0	3 (1)	1 (0)	5 (2)
Digestive System				
Constipation	5 (2)	7 (2)	6 (2)	3 (1)
Diarrhea	5 (2)	2 (1)	6 (2)	8 (2)

TABLE 2: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY OF ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625/2.5 continuous (N=331)	PREMPRO 0.45/1.5 continuous (N=331)	PREMPRO 0.3/1.5 continuous (N=327)	PLACEBO daily (N=332)
Dyspepsia	10 (3)	9 (3)	6 (2)	14 (4)
Flatulence	16 (5)	18 (5)	13 (4)	8 (2)
Increased appetite	6 (2)	2 (1)	0	2 (1)
Nausea	13 (4)	13 (4)	16 (5)	16 (5)
Metabolic and nutritional				
Peripheral edema	7 (2)	8 (2)	4 (1)	3 (1)
Weight gain	9 (3)	8 (2)	6 (2)	14 (4)
Musculoskeletal System				
Arthralgia	2 (1)	3 (1)	3 (1)	5 (2)
Leg cramps	13 (4)	7 (2)	10 (3)	4 (1)
Nervous System				
Anxiety	5 (2)	4 (1)	1 (0)	4 (1)
Depression	23 (7)	11 (3)	11 (3)	17 (5)
Dizziness	3 (1)	8 (2)	6 (2)	5 (2)
Emotional lability	10 (3)	10 (3)	9 (3)	8 (2)
Insomnia	8 (2)	7 (2)	9 (3)	14 (4)
Nervousness	6 (2)	3 (1)	4 (1)	6 (2)
Skin and Appendages				
Acne	7 (2)	3 (1)	0	3 (1)
Alopecia	1 (0)	6 (2)	4 (1)	2 (1)
Pruritus	8 (2)	10 (3)	9 (3)	3 (1)
Rash	0	6 (2)	4 (1)	2 (1)
Skin discoloration	5 (2)	1 (0)	3 (1)	1 (0)
Sweating	3 (1)	1 (0)	0	4 (1)
Urogenital System				
Breast disorder	7 (2)	6 (2)	5 (2)	6 (2)
Breast enlargement	18 (5)	9 (3)	5 (2)	3 (1)
Breast neoplasm	8 (2)	7 (2)	5 (2)	7 (2)
Breast pain	87 (26)	66 (20)	41 (13)	26 (8)
Cervix disorder	7 (2)	2 (1)	2 (1)	0
Dysmenorrhea	14 (4)	18 (5)	9 (3)	2 (1)
Hematuria	4 (1)	3 (1)	1 (0)	2 (1)
Leukorrhea	7 (2)	14 (4)	9 (3)	6 (2)
Metrorrhagia	7 (2)	14 (4)	4 (1)	1 (0)
Urinary tract infection	0	1 (0)	1 (0)	4 (1)
Uterine spasm	13 (4)	11 (3)	7 (2)	2 (1)
Vaginal dryness	2 (1)	1 (0)	0	6 (2)
Vaginal hemorrhage	18 (5)	14 (4)	7 (2)	0
Vaginal moniliasis	13 (4)	11 (3)	8 (2)	5 (2)

TABLE 2: ALL TREATMENT RELATED ADVERSE REACTIONS AT A FREQUENCY OF ≥ 1 PERCENT

Body System Adverse event	PREMPRO 0.625/2.5 continuous (N=331)	PREMPRO 0.45/1.5 continuous (N=331)	PREMPRO 0.3/1.5 continuous (N=327)	PLACEBO daily (N=332)
Vaginitis	6 (2)	8 (2)	7 (2)	1 (0)

In addition, the following events were considered as related to the study drug with an incidence less than 1 percent, including accidental injury, infection, myalgia, cough increased, rhinitis, sinusitis, and upper respiratory infection.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of PREMPRO or PREMPHASE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System

Abnormal uterine bleeding, dysmenorrhea or pelvic pain, increase in size of uterine leiomyomata, vaginitis, vaginal candidiasis, amenorrhea, changes in cervical secretion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

Cardiovascular

Deep and superficial venous thrombosis, pulmonary embolism, superficial thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

Gastrointestinal

Nausea, vomiting, abdominal pain, bloating, cholestatic jaundice, increased incidence of gallbladder disease, pancreatitis, changes in appetite, ischemic colitis.

Skin

Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, loss of scalp hair, hirsutism, pruritus, urticaria, rash, acne.

Eyes

Retinal vascular thrombosis, intolerance of contact lenses.

Central Nervous System

Headache, migraine, dizziness, mental depression, exacerbation of chorea, mood disturbances, anxiety, irritability, exacerbation of epilepsy, dementia, growth potentiation of benign meningioma.

Miscellaneous

Increase or decrease in weight, arthralgia, glucose intolerance, edema, changes in libido, exacerbation of asthma, increased triglycerides, hypersensitivity.

Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

7 DRUG INTERACTIONS

Data from a single-dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are coadministered. No other clinical drug-drug interaction studies have been conducted with CE plus MPA.

7.1 Metabolic Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

Aminoglutethimide administered concomitantly with MPA may significantly depress the bioavailability of MPA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

PREMPRO and PREMPHASE should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.3 Nursing Mothers

PREMPRO and PREMPHASE should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving these drugs. Caution should be exercised when PREMPRO or PREMPHASE is administered to a nursing woman.

8.4 Pediatric Use

PREMPRO and PREMPHASE are not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing PREMPRO or PREMPHASE to determine whether those over 65 years of age differ from younger subjects in their response to PREMPRO or PREMPHASE.

The Women's Health Initiative Studies

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.6)]*.

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.6)]*.

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin or estrogen-alone when compared to placebo *[see Warnings and Precautions (5.3), and Clinical Studies (14.7)]*.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Warnings and Precautions (5.3), and Clinical Studies (14.7)]*.

8.6 Renal Impairment

The effects of renal impairment on the pharmacokinetics of PREMPRO or PREMPHASE have not been studied.

8.7 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of PREMPRO or PREMPHASE have not been studied.

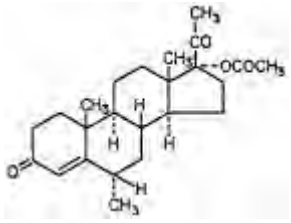
10 OVERDOSAGE

Overdosage of estrogen plus progestin may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of PREMPRO or PREMPHASE therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

Premarin (conjugated estrogens tablets, USP) for oral administration contains a mixture obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol and 17 β-dihydroequilin.

Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odorless, crystalline powder, stable in air, melting between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water. The chemical name for MPA is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. Its molecular formula is $C_{24}H_{34}O_4$, with a molecular weight of 386.53. Its structural formula is:



PREMPRO 0.3 mg/1.5 mg and 0.45 mg/1.5 mg tablets contain the following inactive ingredients: calcium phosphate tribasic, microcrystalline cellulose, carnauba wax, hypromellose, hydroxypropyl cellulose, sucrose, Eudragit NE 30D, lactose monohydrate, magnesium stearate, polyethylene glycol, titanium dioxide, yellow iron oxide, propylene glycol and black iron oxide.

PREMPRO 0.625 mg/2.5 mg tablets contain the following inactive ingredients: calcium phosphate tribasic, microcrystalline cellulose, hypromellose, hydroxypropyl cellulose, sucrose, Eudragit NE 30D, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, titanium dioxide, red iron oxide, yellow iron oxide, and black iron oxide.

PREMPRO 0.625 mg/5 mg tablets contain the following inactive ingredients: calcium phosphate tribasic, carnauba wax, Eudragit NE 30D, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, and black iron oxide.

PREMPHASE

Each maroon Premarin tablets for oral administration contain 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, and FD&C Red No. 40. These tablets comply with USP Dissolution Test 5.

Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens, 5 mg of medroxyprogesterone acetate, and the following inactive ingredients: calcium phosphate tribasic, carnauba wax, Eudragit NE 30D, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sucrose, titanium dioxide, FD&C Blue No. 2, and black iron oxide.

PREMPRO

Tablet Strength	Tablet Color Contains
0.3 mg/1.5 mg	Yellow iron oxide and black iron oxide
0.45 mg/1.5 mg	Yellow iron oxide and black iron oxide
0.625 mg/2.5 mg	Red iron oxide, yellow iron oxide, and black iron oxide
0.625 mg/5 mg	FD&C Blue No. 2 and black iron oxide

PREMPHASE

Tablet Strength	Tablet Color Contains
0.625 mg	FD&C Blue No. 2 and FD&C Red No. 40
0.625 mg/5 mg	FD&C Blue No. 2 and black iron oxide

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Parenterally administered medroxyprogesterone acetate (MPA) inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation; although available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses. MPA may achieve its beneficial effect on the endometrium in part by decreasing nuclear estrogen receptors and suppression of epithelial DNA synthesis in endometrial tissue. Androgenic and anabolic effects of MPA have been noted, but the drug is apparently devoid of significant estrogenic activity.

12.2 Pharmacodynamics

Currently, there are no pharmacodynamic data known for PREMPRO or PREMPHASE tablets.

12.3 Pharmacokinetics

Absorption

PREMPRO and PREMPHASE contain a formulation of medroxyprogesterone acetate (MPA) that is immediately released and conjugated estrogens that are slowly released over several hours. Conjugated estrogens are water-soluble and are well-absorbed from the gastrointestinal tract after release from the drug formulation. MPA is well absorbed from the gastrointestinal tract. Table 3 and Table 4 summarize the mean pharmacokinetic parameters for select unconjugated and conjugated estrogens and medroxyprogesterone acetate following administration of PREMPRO to healthy, postmenopausal women.

TABLE 3: PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	2 x 0.625 mg CE/2.5 mg MPA Combination Tablets (n = 54)				2 x 0.625 mg CE/5 mg MPA Combination Tablets (n = 51)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens								
Estrone	175 (23)	7.6 (24)	31.6 (23)	5358 (34)	124 (43)	10 (35)	62.2 (137)	6303 (40)
BA* -Estrone	159 (26)	7.6 (24)	16.9 (34)	3313 (40)	104 (49)	10 (35)	26.0 (100)	3136 (51)
Equilin	71 (31)	5.8 (34)	9.9 (35)	951 (43)	54 (43)	8.9 (34)	15.5 (53)	1179 (56)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens								
Total Estrone	6.6 (38)	6.1 (28)	20.7 (34)	116 (59)	6.3 (48)	9.1 (29)	23.6 (36)	151 (42)
BA* -Total Estrone	6.4 (39)	6.1 (28)	15.4 (34)	100 (57)	6.2 (48)	9.1 (29)	20.6 (35)	139 (40)
Total Equilin	5.1 (45)	4.6 (35)	11.4 (25)	50 (70)	4.2 (52)	7.0 (36)	17.2 (131)	72 (50)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Medroxyprogesterone Acetate								
MPA	1.5 (40)	2.8 (54)	37.6 (30)	37 (30)	4.8 (31)	2.4 (50)	46.3 (39)	102 (28)

BA* = Baseline adjusted
C_{max} = peak plasma concentration
t_{max} = time peak concentration occurs
$t_{1/2}$ = apparent terminal-phase disposition half-life ($0.693/\lambda_z$)
AUC = total area under the concentration-time curve

TABLE 4. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE) AND MEDROXYPROGESTERONE ACETATE (MPA)

DRUG	4 x 0.45 mg CE/1.5 mg MPA Combination (n = 65)			
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (pg/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (pg•h/mL)
Unconjugated Estrogens				
Estrone	149 (35)	8.9 (35)	37.5 (35)	6641 (39)
BA* -Estrone	130 (40)	8.9 (35)	21.2 (35)	3799 (47)
Equilin	83 (38)	8.3 (48)	15.9 (44)	1889 (40)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Conjugated Estrogens				
Total Estrone	5.4 (49)	7.9 (48)	22.4 (53)	119 (48)
BA* -Total Estrone	5.2 (48)	7.9 (48)	15.1 (29)	100 (47)
Total Equilin	4.3 (42)	6.5 (45)	11.6 (31)	74 (48)
PK Parameter Arithmetic Mean (%CV)	**C_{max}** (ng/mL)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC** (ng•h/mL)
Medroxyprogesterone Acetate				
MPA	0.7 (66)	2.0 (52)	26.2 (35)	5.0 (61)

BA* = Baseline adjusted
C_{max} = peak plasma concentration
t_{max} = time peak concentration occurs
$t_{1/2}$ = apparent terminal-phase disposition half-life ($0.693/\lambda_z$)
AUC = total area under the concentration-time curve

Food-Effect: Single dose studies in healthy, postmenopausal women were conducted to investigate any potential drug interaction when PREMPRO or PREMPHASE is administered with a high-fat breakfast. Administration with food decreased the C_{max} of total estrone by 18 to 34 percent and increased total equilin C_{max} by 38 percent compared to the fasting state, with no other effect on the rate or extent of absorption of other conjugated or unconjugated estrogens. Administration with food approximately doubles MPA C_{max} and increases MPA AUC by approximately 20 to 30 percent.

Dose Proportionality: The C_{max} and AUC values for MPA observed in two separate pharmacokinetic studies conducted with 2 PREMPRO 0.625 mg/2.5 mg or 2 PREMPRO or

PREMPHASE 0.625 mg/5 mg tablets exhibited nonlinear dose proportionality; doubling the MPA dose from 2 x 2.5 to 2 x 5 mg increased the mean C_{max} and AUC by 3.2- and 2.8-fold, respectively.

The dose proportionality of estrogens and medroxyprogesterone acetate was assessed by combining pharmacokinetic data across another two studies totaling 61 healthy, postmenopausal women. Single conjugated estrogens doses of 2 x 0.3 mg, 2 x 0.45 mg, or 2 x 0.625 mg were administered either alone or in combination with medroxyprogesterone acetate doses of 2 x 1.5 mg or 2 x 2.5 mg. Most of the estrogen components demonstrated dose proportionality; however, several estrogen components did not. Medroxyprogesterone acetate pharmacokinetic parameters increased in a dose-proportional manner.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to SHBG and albumin. MPA is approximately 90 percent bound to plasma proteins, but does not bind to SHBG.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Metabolism and elimination of MPA occur primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Most metabolites of MPA are excreted as glucuronide conjugates, with only minor amounts excreted as sulfates.

Use in Specific Populations

No pharmacokinetic studies were conducted in specific populations, including patients with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breasts, uterus, cervix, vagina, testis, and liver.

14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2,805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups of either placebo or conjugated estrogens, with or without medroxyprogesterone acetate. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least seven moderate to severe hot flushes daily, or at least 50 moderate to severe hot flushes during the week before randomization. With PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg, the relief of both the frequency and severity of moderate to severe vasomotor symptoms was shown to be statistically improved compared to placebo at weeks 4 and 12. Table 5 shows the adjusted mean number of hot flushes in the PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, 0.3 mg/1.5 mg, and placebo groups during the initial 12-week period.

TABLE 5: SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY – MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP – PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, LAST OBSERVATION CARRIED FORWARD (LOCF)

Treatment[a] (No. of Patients)	----------No. of Hot Flushes/Day----------			
Time Period (week)	Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Values vs. Placebo[b]
0.625 mg/2.5 mg (n = 34)				
4	11.98 ± 3.54	3.19 ± 3.74	-8.78 ± 4.72	<0.001
12	11.98 ± 3.54	1.16 ± 2.22	-10.82 ± 4.61	<0.001
0.45 mg/1.5 mg (n = 29)				
4	12.61 ± 4.29	3.64 ± 3.61	-8.98 ± 4.74	<0.001
12	12.61 ± 4.29	1.69 ± 3.36	-10.92 ± 4.63	<0.001

TABLE 5: SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY – MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP – PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, LAST OBSERVATION CARRIED FORWARD (LOCF)

Treatment[a] (No. of Patients)	----------No. of Hot Flushes/Day----------			
Time Period (week)	Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Values vs. Placebo[b]
0.3 mg/1.5 mg (n = 33)				
4	11.30 ± 3.13	3.70 ± 3.29	-7.60 ± 4.71	<0.001
12	11.30 ± 3.13	1.31 ± 2.82	-10.00 ± 4.60	<0.001
Placebo (n = 28)				
4	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 4.71	-
12	11.69 ± 3.87	5.71 ± 5.22	-5.98 ± 4.60	-

[a] Identified by dosage (mg) of Premarin/MPA or placebo.
[b] There were no statistically significant differences between the 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg groups at any time period.

14.2 Effects on Vulvar and Vaginal Atrophy

Results of vaginal maturation indexes at cycles 6 and 13 showed that the differences from placebo were statistically significant ($p < 0.001$) for all treatment groups.

14.3 Effects on the Endometrium

In a 1-year clinical trial of 1,376 women (average age 54 ± 4.6 years) randomized to PREMPRO 0.625 mg/2.5 mg (n = 340), PREMPRO 0.625 mg/5 mg (n = 338), PREMPHASE 0.625 mg/5 mg (n = 351), or Premarin 0.625 mg alone (n = 347), results of evaluable biopsies at 12 months (n = 279, 274, 277, and 283, respectively) showed a reduced risk of endometrial hyperplasia in the two PREMPRO treatment groups (less than 1 percent) and in the PREMPHASE treatment group (less than 1 percent; 1 percent when focal hyperplasia was included) compared to the Premarin group (8 percent; 20 percent when focal hyperplasia was included), see Table 6.

TABLE 6: INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER ONE YEAR OF TREATMENT

	Groups			
	PREMPRO 0.625 mg/ 2.5 mg	PREMPRO 0.625 mg/ 5 mg	PREMPHASE 0.625 mg/ 5 mg	Premarin 0.625 mg
Total number of patients	340	338	351	347
Number of patients with evaluable biopsies	279	274	277	283
No. (%) of patients with biopsies:				
• All focal and non-focal hyperplasia	2 (<1)*	0 (0)*	3 (1)*	57 (20)
• Excluding focal cystic hyperplasia	2 (<1)*	0 (0)*	1 (<1)*	25 (8)

* Significant ($p < 0.001$) in comparison with Premarin (0.625 mg) alone.

In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, 2,001 women (average age 53.3 ± 4.9 years), of whom 88 percent were Caucasian, were treated with either Premarin 0.625 mg alone (n = 348), Premarin 0.45 mg alone (n = 338), Premarin 0.3 mg alone (n = 326) or PREMPRO 0.625 mg/2.5 mg (n = 331), PREMPRO 0.45 mg/1.5 mg (n = 331) or PREMPRO 0.3 mg/1.5 mg (n = 327). Results of evaluable endometrial biopsies at 12 months showed a reduced risk of endometrial hyperplasia or cancer in the PREMPRO treatment groups compared with the corresponding Premarin alone treatment groups, except for the PREMPRO 0.3 mg/1.5 mg and Premarin 0.3 mg alone groups, in each of which there was only 1 case, see Table 7.

No endometrial hyperplasia or cancer was noted in those patients treated with the continuous combined regimens who continued for a second year in the osteoporosis and metabolic substudy of the HOPE study, see Table 8.

TABLE 7: INCIDENCE OF ENDOMETRIAL HYPERPLASIA/CANCER[a] AFTER ONE YEAR OF TREATMENT[b]

	Groups					
Patient	Prempro 0.625 mg/ 2.5 mg	Premarin 0.625 mg	Prempro 0.45 mg/ 1.5 mg	Premarin 0.45 mg	Prempro 0.3 mg/ 1.5 mg	Premarin 0.3 mg
Total number of patients	331	348	331	338	327	326
Number of patients with evaluable biopsies	278	249	272	279	271	269
No. (%) of patients with biopsies:						
• Hyperplasia/cancer[a] (consensus[c])	0 (0)[d]	20 (8)	1 (<1)[a,d]	9 (3)	1 (<1)[e]	1 (<1)[a]

[a] All cases of hyperplasia/cancer were endometrial hyperplasia, except for 1 patient in the Premarin 0.3 mg group diagnosed with endometrial cancer based on endometrial biopsy and 1 patient in the Premarin/MPA 0.45 mg/1.5 mg group diagnosed with endometrial cancer based on endometrial biopsy.
[b] Two (2) primary pathologists evaluated each endometrial biopsy. Where there was lack of agreement on the presence or absence of hyperplasia/cancer between the two, a third pathologist adjudicated (consensus).
[c] For an endometrial biopsy to be counted as consensus endometrial hyperplasia or cancer, at least 2 pathologists had to agree on the diagnosis.
[d] Significant ($p < 0.05$) in comparison with corresponding dose of Premarin alone.
[e] Non-significant in comparison with corresponding dose of Premarin alone.

TABLE 8: OSTEOPOROSIS AND METABOLIC SUBSTUDY, INCIDENCE OF ENDOMETRIAL HYPERPLASIA/CANCER[a] AFTER TWO YEARS OF TREATMENT[b]

	----------Groups----------					
Patient	Prempro 0.625 mg/ 2.5 mg	Premarin 0.625 mg	Prempro 0.45 mg/ 1.5 mg	Premarin 0.45 mg	Prempro 0.3 mg/ 1.5 mg	Premarin 0.3 mg
Total number of patients	75	65	75	74	79	73
Number of patients with evaluable biopsies	62	55	69	67	75	63
No. (%) of patients with biopsies:						
• Hyperplasia/cancer[a] (consensus[c])	0 (0)[d]	15 (27)	0 (0)[d]	10 (15)	0 (0)[d]	2 (3)

[a] All cases of hyperplasia/cancer were endometrial hyperplasia in patients who continued for a second year in the osteoporosis and metabolic substudy of the HOPE study.
[b] Two (2) primary pathologists evaluated each endometrial biopsy. Where there was lack of agreement on the presence or absence of hyperplasia/cancer between the two, a third pathologist adjudicated (consensus).
[c] For an endometrial biopsy to be counted as consensus endometrial hyperplasia or cancer, at least 2 pathologists had to agree on the diagnosis.
[d] Significant ($p < 0.05$) in comparison with corresponding dose of Premarin alone.

14.4 Effects on Uterine Bleeding or Spotting

The effects of PREMPRO on uterine bleeding or spotting, as recorded on daily diary cards, were evaluated in 2 clinical trials. Results are shown in Figures 1 and 2.

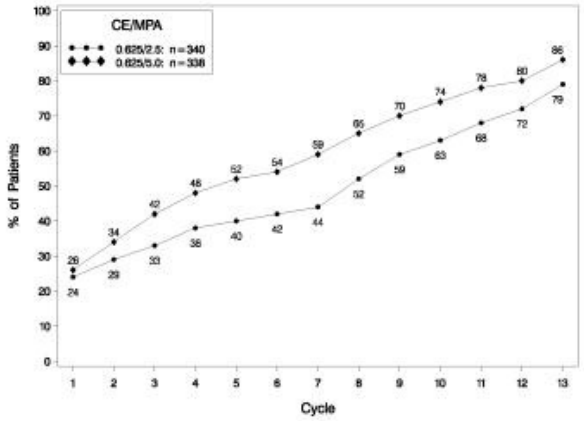


FIGURE 1. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING AT A GIVEN CYCLE THROUGH CYCLE 13 INTENT-TO-TREAT POPULATION, LOCF

Note: The percentage of patients who were amenorrheic in a given cycle and through cycle 13 is shown. If data were missing, the bleeding value from the last reported day was carried forward (LOCF).

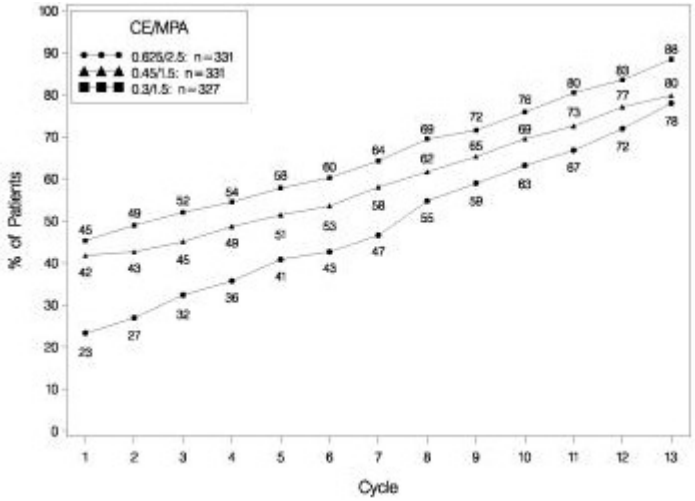


FIGURE 2. PATIENTS WITH CUMULATIVE AMENORRHEA OVER TIME PERCENTAGES OF WOMEN WITH NO BLEEDING OR SPOTTING AT A GIVEN CYCLE THROUGH CYCLE 13 INTENT-TO-TREAT POPULATION, LOCF

Note: The percentage of patients who were amenorrheic in a given cycle and through cycle 13 is shown. If data were missing, the bleeding value from the last reported day was carried forward (LOCF).

14.5 Effects on Bone Mineral Density

Health and Osteoporosis, Progestin and Estrogen (HOPE) Study

The HOPE study was a double-blind, randomized, placebo/active-drug-controlled, multicenter study of healthy postmenopausal women with an intact uterus. Subjects (mean age 53.3 ± 4.9 years) were 2.3 ± 0.9 years on average since menopause and took one 600 mg tablet of elemental calcium (Caltrate™) daily. Subjects were not given Vitamin D supplements. They were treated with PREMPRO 0.625 mg/2.5 mg, 0.45 mg/1.5 mg or 0.3 mg/1.5 mg, comparable doses of Premarin alone, or placebo. Prevention of bone loss was assessed by measurement of bone mineral density (BMD), primarily at the anteroposterior lumbar spine (L_2 to L_4). Secondarily, BMD measurements of the total body, femoral neck, and trochanter were also analyzed. Serum osteocalcin, urinary calcium, and N-telopeptide were used as bone turnover markers (BTM) at cycles 6, 13, 19, and 26.

Intent-to-treat subjects

All active treatment groups showed significant differences from placebo in each of the four BMD endpoints. These significant differences were seen at cycles 6, 13, 19, and 26.

The percent changes from baseline to final evaluation are shown in Table 9.

TABLE 9: PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LOCF

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs. Placebo
L_2 to L_4 BMD				
0.625/2.5	81	1.14 ± 0.16	3.28 ± 0.37	<0.001
0.45/1.5	89	1.16 ± 0.14	2.18 ± 0.35	<0.001
0.3/1.5	90	1.14 ± 0.15	1.71 ± 0.35	<0.001
Placebo	85	1.14 ± 0.14	-2.45 ± 0.36	
Total body BMD				
0.625/2.5	81	1.14 ± 0.08	0.87 ± 0.17	<0.001
0.45/1.5	89	1.14 ± 0.07	0.59 ± 0.17	<0.001
0.3/1.5	91	1.13 ± 0.08	0.60 ± 0.16	<0.001
Placebo	85	1.13 ± 0.08	-1.50 ± 0.17	
Femoral neck BMD				
0.625/2.5	81	0.89 ± 0.14	1.62 ± 0.46	<0.001
0.45/1.5	89	0.89 ± 0.12	1.48 ± 0.44	<0.001
0.3/1.5	91	0.86 ± 0.11	1.31 ± 0.43	<0.001
Placebo	85	0.88 ± 0.14	-1.72 ± 0.45	
Femoral trochanter BMD				
0.625/2.5	81	0.77 ± 0.14	3.35 ± 0.59	0.002

TABLE 9: PERCENT CHANGE IN BONE MINERAL DENSITY: COMPARISON BETWEEN ACTIVE AND PLACEBO GROUPS IN THE INTENT-TO-TREAT POPULATION, LOCF

Region Evaluated Treatment Group[a]	No. of Subjects	Baseline (g/cm^2) Mean ± SD	Change from Baseline (%) Adjusted Mean ± SE	p-Value vs. Placebo
0.45/1.5	89	0.76 ± 0.12	2.84 ± 0.57	0.011
0.3/1.5	91	0.76 ± 0.12	3.93 ± 0.56	<0.001
Placebo	85	0.75 ± 0.12	0.81 ± 0.58	

[a] Identified by dosage (mg/mg) of Premarin/MPA or placebo.

Figure 3 shows the cumulative percentage of subjects with percent changes from baseline in spine BMD equal to or greater than the percent change shown on the x-axis.

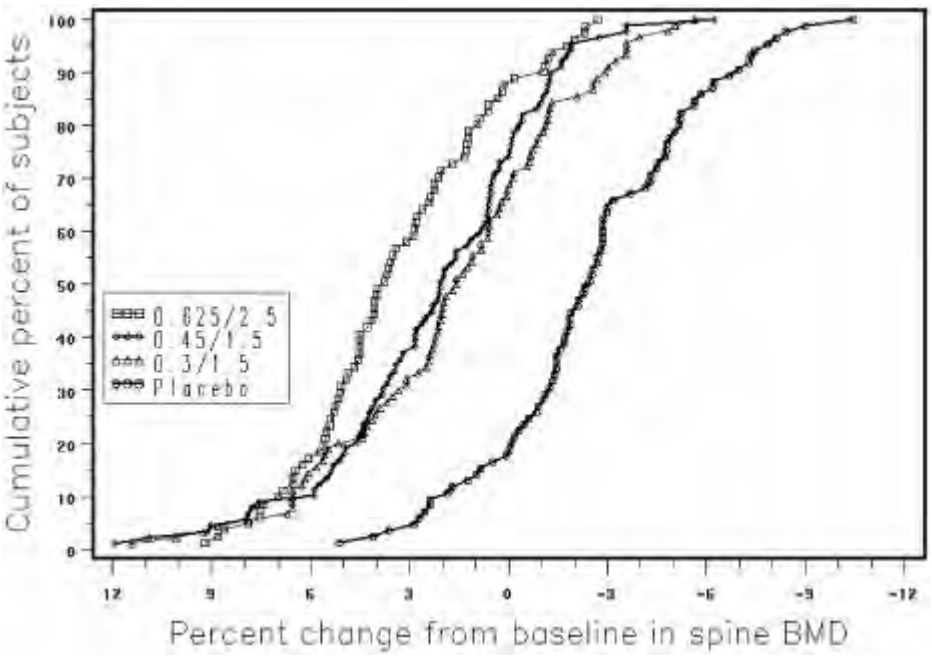


FIGURE 3. CUMULATIVE PERCENT OF SUBJECTS WITH CHANGES FROM BASELINE IN SPINE BMD OF GIVEN MAGNITUDE OR GREATER IN PREMARIN/MPA AND PLACEBO GROUPS

The mean percent changes from baseline in L_2 to L_4 BMD for women who completed the bone density study are shown with standard error bars by treatment group in Figure 4. Significant differences between each of the PREMPRO dosage groups and placebo were found at cycles 6, 13, 19, and 26.

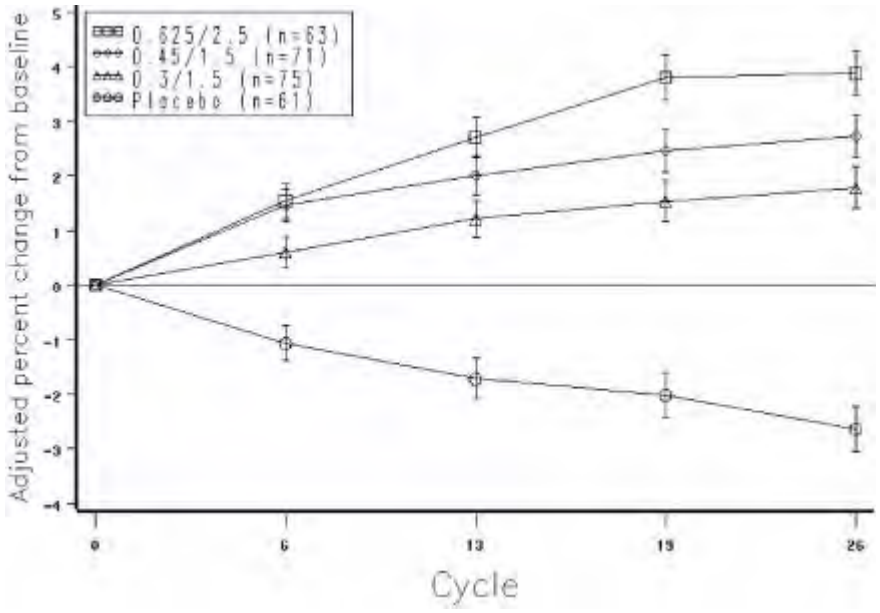


FIGURE 4. ADJUSTED MEAN (SE) PERCENT CHANGE FROM BASELINE AT EACH CYCLE IN SPINE BMD: SUBJECTS COMPLETING IN PREMARIN/MPA GROUPS AND PLACEBO

The bone turnover markers, serum osteocalcin and urinary N-telopeptide, significantly decreased ($p < 0.001$) in all active-treatment groups at cycles 6, 13, 19, and 26 compared with the placebo group. Larger mean decreases from baseline were seen with the active groups than with the placebo group. Significant differences from placebo were seen less frequently in urine calcium; only with PREMPRO 0.625 mg/2.5 mg and 0.45 mg/1.5 mg were there significantly larger mean decreases than with placebo at 3 or more of the 4 time points.

14.6 Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These substudies did not evaluate the effects of CE plus MPA or CE-alone on menopausal symptoms.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 10. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

TABLE 10: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[c])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99–1.53)	41	34
Non-fatal MI	*1.28 (1.00–1.63)*	*31*	*25*
CHD death	*1.10 (0.70–1.75)*	*8*	*8*
All Strokes	1.31 (1.03–1.68)	33	25
Ischemic stroke	*1.44 (1.09–1.90)*	*26*	*18*
Deep vein thrombosis[d]	1.95 (1.43–2.67)	26	13
Pulmonary embolism	2.13 (1.45–3.11)	18	8
Invasive breast cancer[e]	1.24 (1.01–1.54)	41	33
Colorectal cancer	0.61 (0.42–0.87)	10	16
Endometrial cancer[d]	0.81 (0.48–1.36)	6	7
Cervical cancer[d]	1.44 (0.47–4.42)	2	1
Hip fracture	0.67 (0.47–0.96)	11	16
Vertebral fractures[d]	0.65 (0.46–0.92)	11	17
Lower arm/wrist fractures[d]	0.71 (0.59–0.85)	44	62
Total fractures[d]	0.76 (0.69–0.83)	152	199
Overall Mortality[f]	1.00 (0.83-1.19)	52	52
Global Index[g]	1.13 (1.02-1.25)	184	165

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Results are based on centrally adjudicated data.
[c] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[d] Not included in "global index."
[e] Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* breast cancer.
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

[g] A subset of the events was combined in a "global index" defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age, a non-significant trend toward reduced risk for overall mortality *[hazard ratio (HR) 0.69 (95 percent CI, 0.44-1.07)]*.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 11.

Table 11: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[b])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78–1.16)	54	57
Non-fatal MI[c]	*0.91 (0.73–1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71–1.43)*	*16*	*16*
All Strokes[c]	1.33 (1.05–1.68)	45	33
Ischemic stroke[c]	*1.55 (1.19–2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06–2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90–2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62–1.04)	28	34
Colorectal cancer[e]	1.08 (0.75–1.55)	17	16
Hip fracture[c]	0.65 (0.45–0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44–0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47–0.72)	35	59
Total fractures[c,d]	0.71 (0.64–0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88–1.32)	53	50
Overall mortality[c,d]	1.04 (0.88–1.22)	79	75
Global Index[g]	1.02 (0.92–1.13)	206	201

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[c] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[d] Not included in "global index."
[e] Results are based on an average follow-up of 6.8 years.
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a "global index" defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9] The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined.[10]

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy, stratified by age, showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD [HR 0.63 (95 percent CI, 0.36-1.09)] and overall mortality *[HR 0.71 (95 percent CI, 0.46-1.11)]*.

14.7 Women's Health Initiative Memory Study

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years of age; and 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply

to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

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9. Jackson RD, et al. Effects of Conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. *J Bone Miner Res*. 2006;21:817-828.
10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation*. 2006;113:2425-2434.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PREMPRO therapy consists of a single tablet to be taken once daily.

PREMPRO 0.3 mg/1.5 mg

NDC 0046-1105-11, carton includes 1 blister card containing 28 oval, cream tablets.

PREMPRO 0.45 mg/1.5 mg

NDC 0046-1106-11, carton includes 1 blister card containing 28 oval, gold tablets.

PREMPRO 0.625 mg/2.5 mg

NDC 0046-1107-11, carton includes 1 blister card containing 28 oval, peach tablets.

PREMPRO 0.625 mg/5 mg

NDC 0046-1108-11, carton includes 1 blister card containing 28 oval, light-blue tablets.

PREMPHASE therapy consists of two separate tablets; one maroon Premarin tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28.

NDC 0046-2575-12, carton includes 1 blister card containing 28 tablets (14 oval, maroon Premarin tablets and 14 oval, light-blue tablets).

The appearance of PREMPRO tablets is a trademark of Pfizer Inc.

The appearance of PREMARIN tablets is a trademark of Pfizer Inc. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a trademark.

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

17.1 Abnormal Vaginal Bleeding

Inform postmenopausal women of the importance of reporting abnormal vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.2)]*.

17.2 Possible Serious Adverse Reactions with Estrogen Plus Progestin Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen plus progestin therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

17.3 Possible Less Serious but Common Adverse Reactions with Estrogen Plus Progestin Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen plus progestin therapy such as headache, breast pain and tenderness, nausea and vomiting.

This product's label may have been updated. For current package insert and further product information, please visit www.pfizer.com.

LAB-0502-6.1

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AVEED® safely and effectively. See full prescribing information for AVEED®.

AVEED® (testosterone undecanoate) injection, for intramuscular use
CIII
Initial U.S. Approval: 1953

WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS
See full prescribing information for complete boxed warning

- **Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose (5.1).**
- **Following each injection of Aveed, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis (5.1).**
- **Aveed is available only through a restricted program called the Aveed REMS Program (5.2).**

RECENT MAJOR CHANGES

Dosage and Administration (2.2) 08/2021

INDICATIONS AND USAGE

Aveed (testosterone undecanoate) injection is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired) (1)
- Hypogonadotropic hypogonadism (congenital or acquired) (1)

Aveed should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis (1).

Limitations of Use

- Safety and efficacy of Aveed in men with "age-related hypogonadism" have not been established (1).
- Safety and efficacy of Aveed in males less than 18 years old have not been established (1, 8.4).

DOSAGE AND ADMINISTRATION

- Prior to initiating Aveed, confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range (2).
- For intramuscular use only (2.1).
- Three (3) mL (750 mg) is to be injected intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter (2.1).
- Following each injection of Aveed, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis (2.3).
- Inject Aveed deeply into the gluteal muscle following the usual precautions for intramuscular administration of oily solutions (2.3).

DOSAGE FORMS AND STRENGTHS

750 mg/3 mL (250 mg/mL) testosterone undecanoate sterile injectable solution is provided in an amber glass, single use vial with silver-colored crimp seal and gray plastic cap (3).

CONTRAINDICATIONS

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate (4, 5.3).
- Women who are pregnant. Testosterone may cause fetal harm (4, 5.8, 8.1, 8.2).
- Known hypersensitivity to Aveed or its ingredients (testosterone undecanoate, refined castor oil, benzyl benzoate) (4).

WARNINGS AND PRECAUTIONS

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH (5.3).
- Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE (5.5).
- Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy (5.6).
- Exogenous administration of androgens may lead to azoospermia (5.9).
- Edema with or without congestive heart failure may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.11).
- Sleep apnea may occur in those with risk factors (5.13).
- Monitor prostatic specific antigen (PSA), hemoglobin, hematocrit, and lipid concentrations periodically (5.3, 5.4, 5.14).

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥2%) are acne, injection site pain, prostatic specific antigen (PSA) increased, estradiol increased, hypogonadism, fatigue, irritability, hemoglobin increased, insomnia, and mood swings (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals at 1-800-462-3636 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Androgens may decrease blood glucose, and therefore may decrease insulin requirements in diabetic patients (7.1).
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of international normalized ratio (INR) and prothrombin time is recommended in patients taking warfarin (7.2).
- Use of testosterone with corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3).

USE IN SPECIFIC POPULATIONS

Geriatric Patients: There are insufficient long-term safety data to assess the potential risks of cardiovascular disease and prostate cancer (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS

- **Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose *[see Warnings and Precautions (5.1)]*.**
- **Following each injection of AVEED, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis *[see Warnings and Precautions (5.1)]*.**
- **Because of the risks of serious POME reactions and anaphylaxis, AVEED is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the AVEED REMS Program *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

AVEED is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

AVEED should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of POME and anaphylaxis.

Limitations of Use

- Safety and efficacy of AVEED in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
- Safety and efficacy of AVEED in males less than 18 years old have not been established *[see Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

Prior to initiating AVEED, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least 2 separate days and that these serum testosterone concentrations are below the normal range.

2.1 Dosage

AVEED is for intramuscular use only. Dosage titration is not necessary.

Inject AVEED deeply into the gluteal muscle following the usual precautions for intramuscular administration; care must be taken to avoid intravascular injection *[see Dosage and Administration (2.3)]*. Intravascular injection of AVEED may lead to POME *[see Warnings and Precautions (5.1)]*.

The recommended dose of AVEED is 3 mL (750 mg) injected intramuscularly, followed by 3 mL (750 mg) injected after 4 weeks, then 3 mL (750 mg) injected every 10 weeks thereafter.

2.2 Preparation Instructions

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

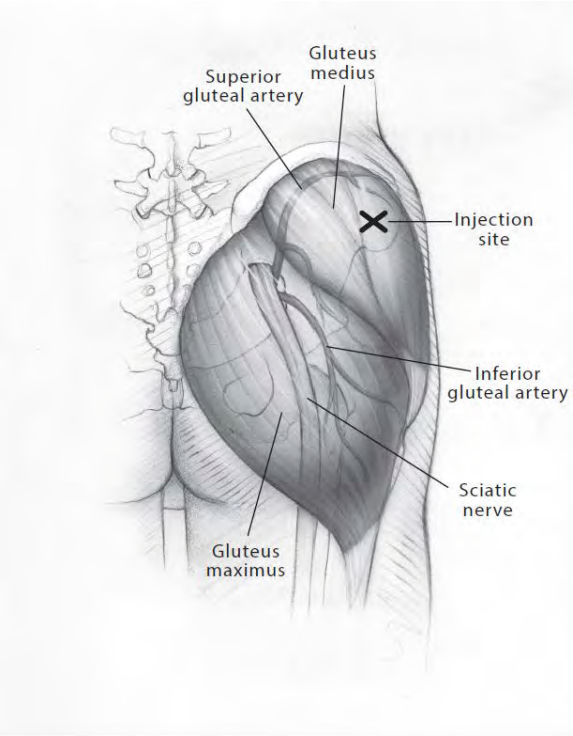
Carefully remove the gray plastic cap from the top of the vial by lifting it up from the edges with your fingers or by pushing the bottom edge of the cap upward using the top of your thumb. Remove only the gray plastic cap while leaving the aluminum metal ring and crimp seal around the gray rubber stopper in place. To facilitate the removal of medication from the vial, attach an 18-gauge needle and draw 3 mL of air into the syringe. Hold the needle at a 45° angle to the stopper with the bevel in the up orientation. Inject through the gray rubber stopper into the vial to create positive pressure within the vial chamber.

Withdraw 3 mL (750 mg) of AVEED solution from the vial. Expel excess air bubbles from the syringe. Replace the syringe needle used to draw up the solution from the vial with a new intramuscular needle and inject. Discard any unused portion in the vial.

2.3 Administration Instructions

The site for injection for AVEED is the *gluteus medius* muscle site located in the upper outer quadrant of the buttock. Care must be taken to avoid the needle hitting the superior gluteal arteries and sciatic nerve. Between consecutive injections, alternate the injection site between left and right buttock.

Figure 1: Identifying the Injection Site



Following antiseptic skin preparation, enter the muscle and maintain the syringe at a 90° angle with the needle in its deeply imbedded position. Grasp the barrel of the syringe firmly with one hand. With the other hand, pull back on the plunger and aspirate for several seconds to ensure that no blood appears. If any blood is drawn into the syringe, immediately withdraw and discard the syringe and prepare another dose.

If no blood is aspirated, reinforce the current needle position to avoid any movement of the needle and slowly (over 60 to 90 seconds) depress the plunger carefully and at a constant rate, until all the medication has been delivered. Be sure to depress the plunger completely with sufficient controlled force. Withdraw the needle.

Immediately upon removal of the needle from the muscle, apply gentle pressure with a sterile pad to the injection site. If there is bleeding at the site of injection, apply a bandage.

Following each injection of AVEED, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

750 mg/3 mL (250 mg/mL) testosterone undecanoate sterile injectable solution is provided in an amber glass, single use vial with silver-colored crimp seal and gray plastic cap.

4 CONTRAINDICATIONS

AVEED should not be used in any of the following patients:

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.3)]*.
- Women who are pregnant. Testosterone can cause virilization of the female fetus when administered to a pregnant woman *[see Use in Specific Populations (8.1, 8.2)]*.
- Men with known hypersensitivity to AVEED or any of its ingredients (testosterone undecanoate, refined castor oil, benzyl benzoate).

5 WARNINGS AND PRECAUTIONS

5.1 Serious Pulmonary Oil Microembolism (POME) Reactions and Anaphylaxis

Serious POME reactions, involving cough, urge to cough, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope, have been reported to occur during or immediately after the injection of intramuscular testosterone undecanoate 1000 mg (4 mL). The majority of these events lasted a few minutes and resolved with supportive measures; however, some lasted up to several hours and some required emergency care and/or hospitalization. To minimize the risk of intravascular injection of AVEED, care should be taken to inject the preparation deeply into the gluteal muscle, being sure to follow the recommended procedure for intramuscular administration *[see Dosage and Administration (2.2, 2.3) and Adverse Reactions (6.2)]*.

In addition to serious POME reactions, episodes of anaphylaxis, including life-threatening reactions, have also been reported to occur following the injection of intramuscular testosterone undecanoate.

Both serious POME reactions and anaphylaxis can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose. Patients with suspected hypersensitivity reactions to AVEED should not be re-treated with AVEED.

Following each injection of AVEED, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions and anaphylaxis.

5.2 AVEED Risk Evaluation and Mitigation Strategy (REMS) Program

AVEED is available only through a restricted program called the AVEED REMS Program because of the risk of serious POME and anaphylaxis.

Notable requirements of the AVEED REMS Program include the following:

- Healthcare providers who prescribe AVEED must be certified with the REMS Program before ordering or dispensing AVEED.

- Healthcare settings must be certified with the REMS Program and have healthcare providers who are certified before ordering or dispensing AVEED. Healthcare settings must have on-site access to equipment and personnel trained to manage serious POME and anaphylaxis.

Further information is available at www.aveedrems.com or call 1-855-755-0494.

5.3 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

Patients with BPH treated with androgens are at an increased risk of worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.

Patients treated with androgens may be at an increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating and during treatment with androgens *[see Contraindications (4)]*.

5.4 Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require discontinuation of testosterone.

Check hematocrit prior to initiating testosterone treatment. It would be appropriate to re-evaluate the hematocrit 3 to 6 months after starting testosterone treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable level. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.5 Venous Thromboembolism (VTE)

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as AVEED. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with AVEED and initiate appropriate workup and management.

5.6 Cardiovascular Risk

Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use AVEED.

5.7 Abuse of Testosterone and Monitoring of Serum Testosterone Concentrations

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions *[see Drug Abuse and Dependence (9)]*.

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

5.8 Use in Women

Due to lack of controlled evaluations in women and potential virilizing effects, AVEED is not indicated for use in women *[see Contraindications (4) and Use in Specific Populations (8.1, 8.2)]*.

5.9 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including AVEED, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH which could possibly lead to adverse effects on semen parameters including sperm count.

5.10 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. AVEED is not known to produce these adverse effects. Nonetheless, patients should be instructed to report any signs or symptoms of hepatic dysfunction (eg, jaundice). If these occur, promptly discontinue AVEED while the cause is evaluated.

5.11 Edema

Androgens, including AVEED, may promote retention of sodium and water. Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

5.12 Gynecomastia

Gynecomastia occasionally develops and occasionally persists in patients being treated for hypogonadism *[see Adverse Reactions (6.1)]*.

5.13 Sleep Apnea

The treatment of hypogonadal men with testosterone products may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases.

5.14 Lipids

Changes in serum lipid profile may require dose adjustment of lipid lowering drugs or discontinuation of testosterone therapy.

5.15 Hypercalcemia

Androgens, including AVEED, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.16 Decreased Thyroxine-binding Globulin

Androgens, including AVEED, may decrease concentrations of thyroxine-binding globulin, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

AVEED was evaluated in an 84-week clinical study using a dose regimen of 750 mg (3 mL) at initiation, at 4 weeks, and every 10 weeks thereafter in 153 hypogonadal men. The most commonly reported adverse reactions (>2%) were: acne (5.2%), injection site pain (4.6%), prostate specific antigen increased (4.6%), hypogonadism (2.6%) and estradiol increased (2.6%).

Table 1 presents adverse reactions reported by ≥1% of patients in the 84-week clinical study.

Table 1: Adverse Reactions Reported in at Least 1% of Patients in the 84-Week Clinical Study of AVEED

MedDRA Preferred Term	Number of Patients (%)
	AVEED 750 mg (N=153)
Acne	8 (5.2%)
Injection site pain	7 (4.6%)
Prostatic specific antigen increased*	7 (4.6%)
Estradiol increased	4 (2.6%)
Hypogonadism	4 (2.6%)
Fatigue	3 (2%)
Irritability	3 (2%)
Hemoglobin increased	3 (2%)
Insomnia	3 (2%)
Mood swings	3 (2%)
Aggression	2 (1.3%)
Ejaculation disorder	2 (1.3%)
Injection site erythema	2 (1.3%)
Hematocrit increased	2 (1.3%)
Hyperhidrosis	2 (1.3%)
Prostate Cancer	2 (1.3%)
Prostate induration	2 (1.3%)
Weight increased	2 (1.3%)

*Prostate-specific antigen increased defined as a serum PSA concentration >4 ng/mL.

In the 84-week clinical trial, 7 patients (4.6%) discontinued treatment because of adverse reactions. Adverse reactions leading to discontinuation included: hematocrit increased, estradiol increased, prostatic specific antigen increased, prostate cancer, mood swings, prostatic dysplasia, acne, and deep vein thrombosis.

During the 84-week clinical trial, the average serum PSA increased from 1.0 ± 0.8 ng/mL at baseline to 1.5 ± 1.3 ng/mL at the end of study. Fourteen (14) patients (10.9%) in whom the baseline PSA was < 4 ng/mL had a post-baseline serum PSA of > 4 ng/mL during the 84-week treatment period.

A total of 725 hypogonadal men received intramuscular testosterone undecanoate in a total of 7 controlled clinical trials. In these clinical trials, the dose and dose frequency of intramuscular testosterone undecanoate varied from 750 mg to 1000 mg, and from every 9 weeks to every 14 weeks. Several of these clinical trials incorporated additional doses upon initiation of

therapy (eg, loading doses). In addition to those adverse reactions noted in Table 1, the following adverse events were reported by at least 3% of patients in these trials, irrespective of the investigator's assessment of relationship to study medication: sinusitis, prostatitis, arthralgia, nasopharyngitis, upper respiratory tract infection, bronchitis, back pain, hypertension, diarrhea and headache.

Pulmonary Oil Microembolism (POME) and Anaphylaxis in Controlled Clinical Studies

Adverse events attributable to POME and anaphylaxis were reported in a small number of patients in controlled clinical trials. In the 84-week clinical trial of AVEED, 1 patient experienced a mild coughing fit lasting 10 minutes after his third injection, which was retrospectively attributed to POME. In another clinical trial of intramuscular testosterone undecanoate (1000 mg), a hypogonadal male patient experienced the urge to cough and respiratory distress at 1 minute after his tenth injection, which was also retrospectively attributed to POME.

During a review that involved adjudication of all cases meeting specific criteria, 9 POME events in 8 patients and 2 events of anaphylaxis among 3,556 patients treated with intramuscular testosterone undecanoate in 18 clinical trials were judged to have occurred.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of AVEED. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Pulmonary Oil Microembolism (POME) and Anaphylaxis

Serious POME reactions, involving cough, urge to cough, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope, have been reported to occur during or immediately after the injection of intramuscular testosterone undecanoate 1000 mg (4 mL) in post-approval use outside the United States. The majority of these events lasted a few minutes and resolved with supportive measures; however, some lasted up to several hours and some required emergency care and/or hospitalization.

In addition to serious POME reactions, episodes of anaphylaxis, including life-threatening reactions, have also been reported to occur following the injection of intramuscular testosterone undecanoate in post-approval use outside of the United States.

Both serious POME reactions and anaphylaxis have been reported to occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose.

Other Events

The following treatment emergent adverse events or adverse reactions have been identified during post-marketing clinical trials and during post-approval use of intramuscular testosterone undecanoate. In most cases, the dose being used was 1000 mg.

Blood and Lymphatic System Disorders: polycythemia, thrombocytopenia

Cardiac Disorders: angina pectoris, cardiac arrest, cardiac failure, coronary artery disease, coronary artery occlusion, myocardial infarction, tachycardia

Ear and Labyrinth Disorders: sudden hearing loss, tinnitus

Endocrine Disorders: hyperparathyroidism, hypoglycemia

Gastrointestinal Disorders: abdominal pain upper, diarrhea, vomiting

General Disorders and Administrative Site Conditions: chest pain, edema peripheral, injection site discomfort, injection site hematoma, injection site irritation, injection site pain, injection site reaction, malaise, paresthesia, procedural pain

Immune System Disorders: anaphylactic reaction, anaphylactic shock, asthma, dermatitis allergic, hypersensitivity, leukocytoclastic vasculitis

Infections and Infestations: injection site abscess, prostate infection

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood glucose increased, blood pressure increased, blood prolactin increased, blood testosterone decreased, blood testosterone increased, blood triglycerides increased, gamma-glutamyltransferase increased, hematocrit increased, intraocular pressure increased, liver function test abnormal, prostate examination abnormal, prostatic specific antigen increased, transaminases increased

Metabolism and Nutrition Disorders: diabetes mellitus, fluid retention, hyperlipidemia, hypertriglyceridemia

Musculoskeletal and Connective Tissue Disorders: musculoskeletal chest pain, musculoskeletal pain, myalgia, osteopenia, osteoporosis, systemic lupus erythematosus

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): prostate cancer, prostatic intraepithelial neoplasia

Nervous System Disorders: stroke, cerebrovascular insufficiency, reversible ischemic neurological deficiency, transient ischemic attack

Psychiatric Disorders: aggression, anxiety, depression, insomnia, irritability, Korsakoff's psychosis non-alcoholic, male orgasmic disorder, nervousness, restlessness, sleep disorder

Renal and Urinary Disorders: calculus urinary, dysuria, hematuria, nephrolithiasis, pollakiuria, renal colic, renal pain, urinary tract disorder

Reproductive System and Breast Disorders: azoospermia, benign prostatic hyperplasia, breast induration, breast pain, erectile dysfunction, gynecomastia, libido decreased, libido increased, prostate induration, prostatitis, spermatocele, testicular pain

Respiratory, Thoracic and Mediastinal Disorders: asthma, chronic obstructive pulmonary disease, cough, dysphonia, dyspnea, hyperventilation, obstructive airway disorder, pharyngeal edema, pharyngolaryngeal pain, pulmonary microemboli, pulmonary embolism, respiratory distress, rhinitis, sleep apnea syndrome, snoring

Skin and Subcutaneous Tissue Disorders: acne, alopecia, angioedema, angioneurotic edema, dermatitis allergic, erythema, hyperhidrosis, pruritus, rash

Vascular Disorders: cerebral infarction, cerebrovascular accident, circulatory collapse, deep venous thrombosis, hot flush, hypertension, syncope, thromboembolism, thrombosis, venous insufficiency

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens, therefore more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with corticosteroids may result in increased fluid retention and requires careful monitoring, particularly in patients with cardiac, renal or hepatic disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

AVEED is contraindicated in pregnant women. Testosterone is teratogenic and may cause fetal harm based on data from animal studies and its mechanism of action *[see Contraindications (4) and Clinical Pharmacology (12.1)]*. Exposure of a female fetus to androgens may result in varying degrees of virilization. In animal development studies, exposure to testosterone in utero resulted in hormonal and behavioral changes in offspring and structural impairments of reproductive tissues in female and male offspring. These studies did not meet current standards for nonclinical development toxicity studies.

Data

Animal Data

In developmental studies conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used for testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased anogenital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and

increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes.

Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant female rats and their offspring exposed to doses approximately twice those used for testosterone replacement therapy.

8.2 Lactation

Risk Summary

AVEED is not indicated for use in females.

8.3 Females and Males of Reproductive Potential

Infertility

During treatment with large doses of exogenous androgens, including AVEED, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis *[see Warnings and Precautions (5.9)]*, possibly leading to adverse effects on semen parameters including sperm count. Reduced fertility is observed in some men taking testosterone replacement therapy. Testicular atrophy, subfertility, and infertility have also been reported in men who abuse anabolic androgenic steroids *[see Drug Abuse and Dependence (9.2)]*. With either type of use, the impact on fertility may be irreversible.

8.4 Pediatric Use

Safety and effectiveness of AVEED in pediatric patients less than 18 years old have not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients in controlled clinical studies with AVEED to determine whether efficacy or safety in those over 65 years of age differs from younger subjects. Of the153 patients enrolled in the pivotal clinical study utilizing AVEED, 26 (17.0%) were over 65 years of age. Additionally, there are insufficient long-term safety data in geriatric patients to assess the potentially increased risk of cardiovascular disease and prostate cancer.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH *[see Warnings and Precautions (5.3)]*.

8.6 Renal Impairment

No studies were conducted in patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AVEED contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

9.2 Abuse

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse of men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids, and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility, and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9.3 Dependence

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations

- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido, and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

10 OVERDOSAGE

There have been no reports of overdosage in the AVEED clinical trials. There is 1 report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels of up to 11,400 ng/dL with a cerebrovascular accident.

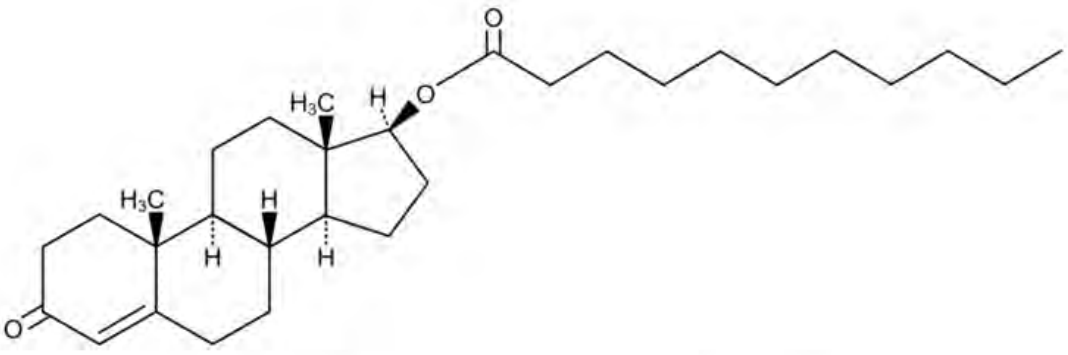
Treatment of overdosage would consist of discontinuation of AVEED together with appropriate symptomatic and supportive care.

11 DESCRIPTION

AVEED (testosterone undecanoate) injection contains testosterone undecanoate (17β-undecanoyloxy-4-androsten-3-one) which is an ester of the androgen, testosterone. Testosterone is formed by cleavage of the ester side chain of testosterone undecanoate.

Testosterone undecanoate is a white to off-white crystalline substance. The empirical formula of testosterone undecanoate is $C_{30}H_{48}O_3$ and a molecular weight of 456.7. The structural formula is:

Figure 2: Testosterone Undecanoate



$C_{30}H_{48}O_3$ MW: 456.7

AVEED is a clear, yellowish, sterile oily solution containing testosterone undecanoate, a testosterone ester, for intramuscular injection. Each single use vial contains 3 mL of 250 mg/mL

testosterone undecanoate solution in a mixture of 1500 mg of benzyl benzoate and 885 mg of refined castor oil.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT) are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; and alterations in body musculature and fat distribution.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has 2 main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.3 Pharmacokinetics

Absorption

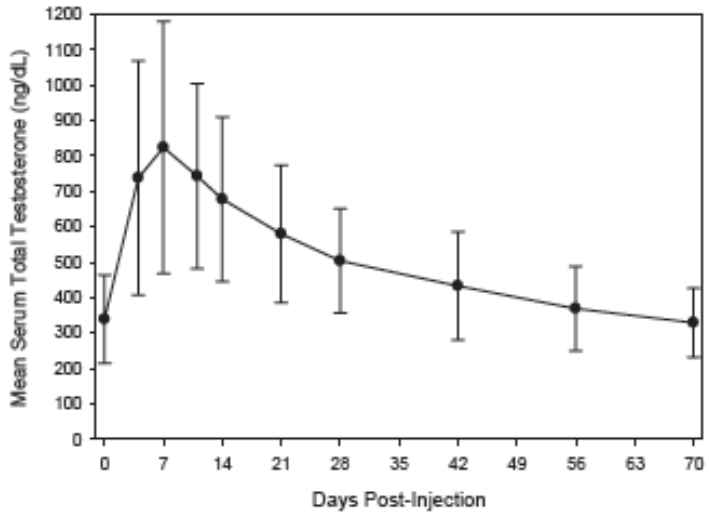
AVEED 750 mg delivers physiologic amounts of testosterone, producing circulation testosterone concentrations that approximate normal concentrations (300-1000 ng/dL) seen in healthy men.

Testosterone esters in oil injected intramuscularly are absorbed from the lipid phase. Cleavage of the undecanoic acid side chain of AVEED by tissue esterases releases testosterone.

Following intramuscular injection of 750 mg of AVEED, serum testosterone concentrations reach a maximum after a median of 7 days (range 4 to 42 days) then slowly decline (Figure 3). Steady-state serum testosterone concentration was achieved with the third injection of AVEED at 14 weeks.

Figure 3 shows the mean serum total testosterone concentration-time profile during the third injection interval (at steady state, 14 to 24 weeks) for hypogonadal men (less than 300 ng/dL) given 750 mg AVEED at initiation, at 4 weeks, and every 10 weeks thereafter. Intramuscular injection of 750 mg of AVEED generates mean steady-state serum total testosterone concentrations in the normal range for 10 weeks.

Figure 3: Mean (SD) Serum Total Testosterone Concentrations (ng/dL) at 14 to 24 Weeks



Distribution

Circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin.

Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free), and the rest is loosely bound to albumin and other proteins.

Metabolism

Testosterone undecanoate is metabolized to testosterone via ester cleavage of the undecanoate group. The mean (SD) maximum concentration of testosterone undecanoate was 90.9 (68.8) ng/dL on Day 4 following injection of AVEED. Testosterone undecanoate was nearly undetectable 42 days following injection of AVEED.

Testosterone is metabolized to various 17-keto steroids through 2 different pathways. The major active metabolites of testosterone are estradiol and DHT.

DHT concentrations increased in parallel with testosterone concentrations during AVEED treatment. Average DHT concentrations during a dosing interval ranged from 244 to 451 ng/dL. The mean DHT to testosterone ratios ranged from 0.05 to 0.07.

Excretion

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. About 90% of a testosterone dose given intramuscularly is excreted in the urine as glucuronic and sulfuric acid-conjugates of testosterone or as metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

Effect of Body Weight and Body Mass Index (BMI)

Analysis of serum testosterone concentrations from 117 hypogonadal men in the 84-week clinical study of AVEED indicated that serum testosterone concentrations achieved were inversely correlated with the patient's body weight. In 60 patients with pretreatment body weight of ≥100 kg, the mean (±SD) serum testosterone average concentration was 426 ± 104 ng/dL. A higher serum testosterone average concentration (568 ± 139 ng/dL) was observed in 57 patients weighing 65 to 100 kg. A similar trend was also observed for maximum serum testosterone concentrations.

In 70 patients with pretreatment BMIs of >30 kg/m^2, the mean (±SD) serum testosterone average concentration was 445 ± 116 ng/dL. Higher serum testosterone average concentrations (579 ± 101 ng/dL and 567± 155ng/dL) were observed in patients with BMIs <26 kg/m^2 and 26 to 30 kg/m^2, respectively. A similar trend was also observed for maximum serum testosterone concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Mutagenesis

AVEED was negative in the in vitro Ames assays, the chromosomal aberration assay in human lymphocytes, and in the in vivo mouse micronucleus assay.

Impairment of Fertility

The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog, and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Testosterone Replacement Therapy

AVEED was evaluated for efficacy in an 84-week, single-arm, open-label, multicenter study of 130 hypogonadal men. Eligible patients weighed at least 65 kg, were 18 years of age and older (mean age 54.2 years), and had a morning serum total testosterone concentration <300 ng/dL (mean screening testosterone concentration 215 ng/dL). Patients were caucasian (74.6%), black (12.3%), Hispanic (10.8%), and of other ethnicities (2.3%). The mean BMI was 32 kg/m^2.

All patients received injections of AVEED 750 mg at baseline, at 4 weeks, and then every 10 weeks thereafter.

The primary endpoint was the percentage of patients with average serum total testosterone concentration (C_{avg}) within the normal range (300-1000 ng/dL) after the third injection, at steady state.

The secondary endpoint was the percentage of patients with maximum total testosterone concentration (C_{max}) above 3 pre-determined limits: greater than 1500 ng/dL, between 1800 and 2499 ng/dL, and greater than 2500 ng/dL.

A total of 117 out of 130 hypogonadal men completed study procedures through Week 24 and were included in the evaluation of testosterone pharmacokinetics after the third AVEED injection. Ninety-four percent (94%) of patients maintained a C_{avg} within the normal range (300 to 1000 ng/dL). The percentages of patients with C_{avg} below the normal range (less than 300 ng/dL) and above the normal range (greater than 1000 ng/dL) were 5.1% and 0.9%, respectively.

Table 2 summarizes the mean (SD) serum total testosterone pharmacokinetic parameters at steady state for these 117 patients.

Table 2: Mean (SD) Serum Total Testosterone Concentrations at Steady State

	AVEED 750 mg (N=117)
$C_{avg\,(0\ to\ 10\ weeks)}$ (ng/dL)	495 (142)
C_{max} (ng/dL)	891 (345)
C_{min} (ng/dL)	324 (99)

C_{avg} = average concentration; C_{max} = maximum concentration; C_{min} = minimum concentration

The percentage of patients with C_{max} >1500 ng/dL was 7.7%. No patient had a C_{max} > 1800 ng/dL.

16 HOW SUPPLIED/STORAGE AND HANDLING

AVEED, NDC 67979-511-43: 750 mg/3 mL (250 mg/mL) testosterone undecanoate sterile injectable solution is provided in an amber glass vial with silver-colored crimp seal and gray plastic cap. Each vial is individually packaged in a carton box.

Store at controlled room temperature 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [See USP controlled room temperature] in its original carton until the date indicated.

Before use, each vial should be visually inspected. Only vials free from particles should be used.

Single Use Vial. Discard unused portion.

17 PATIENT COUNSELING INFORMATION

See **FDA-Approved Medication Guide.**

Advise patients of the following:

17.1 Risks of Serious Pulmonary Oil Microembolism (POME) and Anaphylaxis

- Serious POME reactions, involving cough, urge to cough, shortness of breath, sweating, throat tightening, chest pain, dizziness, and syncope, have been reported to occur during or immediately after the injection of intramuscular testosterone undecanoate. The majority of these events lasted a few minutes and resolved with supportive measures; however, some lasted up to several hours and some required emergency care and/or hospitalization.
- Episodes of anaphylaxis, including life-threatening reactions, have also been reported to occur following the injection of intramuscular testosterone undecanoate.
- Both serious POME reactions and anaphylaxis can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose.
- Advise the patient to read the AVEED REMS information sheet titled ***"What You Need to Know About AVEED® Treatment: A Patient Guide"***.
- Instruct patients to remain at the healthcare setting for 30 minutes after each AVEED injection.

17.2 Men with Known or Suspected Carcinoma of the Prostate or Breast

Men with known or suspected prostate or breast cancer should not use AVEED *[see Contraindications (4)]*.

17.3 Potential Adverse Reactions to Androgens

Patients should be informed that treatment with androgens may lead to adverse reactions which include:

- Changes in urinary habits, such as increased urination at night, trouble starting the urine stream, passing urine many times during the day, having an urge to go the bathroom right away, having a urine accident, or being unable to pass urine or weak urine flow
- Breathing disturbances, including those associated with sleep or excessive daytime sleepiness
- Too frequent or persistent erections of the penis
- Nausea, vomiting, changes in skin color, or ankle swelling

17.4 Patients Should Be Advised of the Following Instructions for Use

- **Read the Medication Guide before starting AVEED therapy and reread the Guide before each injection.**
- Adhere to all recommended monitoring.
- Report any changes in their state of health, such as changes in urinary habits, breathing, sleep, and mood.

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022219Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

Date	February 28, 2013
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	22-219
Applicant	Endo Pharmaceuticals
Date of Submission	August 29, 2013
PDUFA Goal Date	February 28, 2013
Proprietary Name / Established (USAN) names	AVEED™ testosterone undecanoate injection
Dosage forms / Strength	750 mg in 3 mL solution for deep intramuscular injection
Proposed Indication(s)	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommended:	***Approval***

1. Executive Summary

1.1 Brief Summary and Recommendation

AVEED (testosterone undecanoate) injection is intended for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The active ingredient in AVEED is testosterone undecanoate, an ester of testosterone. AVEED also contains refined castor oil and benzyl benzoate. AVEED is administered as a deep intramuscular (IM) injection into the gluteus medius muscle. The dosage strength and the frequency of dosing is 750 mg in 3 mL (250 mg per mL) at start of therapy, then 4 weeks later, then every 10 weeks thereafter.

Multiple preparations of testosterone have been approved by the Agency for replacement therapy in hypogonadal men. Each preparation has its own advantages and disadvantages. AVEED would be an option for testosterone replacement; its benefit over the currently approved injectable T products is fewer injections per year (6 injections per year compared to 13-26 injections per year).

The efficacy of AVEED is supported by a single, open-label, pivotal study using the 750mg Loading regimen (Study IP157-001, Part C). Different dosage strengths and different dose regimens were tested during the development program for AVEED. The AVEED 750 mg Loading regimen (the to-be-marketed regimen) was shown to provide an acceptable level of testosterone replacement. Results of secondary efficacy endpoints correlated with the primary endpoints.

In regard to safety, the adverse reactions associated with intramuscular testosterone undecanoate are consistent with those of all testosterone replacement therapies, except for the rare occurrence of severe post-injection reactions. These events were reported to occur either during or soon after the injection. The manifestations of the post-injection reactions have included: cough, urge to cough, dyspnea, flushing, throat-related symptoms (such as tickling in the throat or sensation of throat tightening), dizziness, and in rare cases, urticaria, syncope,

difficulty breathing, and instability in vital signs. Cases have occurred after the first dose, or after subsequent doses, including after up to 4 years of previously uneventful therapy. Some patients have reported a mild reaction on one occasion followed by a severe reaction on a later occasion.

The exact mechanism for these reactions has not been elucidated, but two etiologies are believed to be underlying:

1) Pulmonary oil microembolism (POME) – as a consequence of the castor oil in AVEED, and
2) Anaphylaxis – likely due to a reaction to the castor oil, the benzyl benzoate and/or the testosterone undecanoate in AVEED.

Since the signs and symptoms overlap, it is often not possible to differentiate serious POME from anaphylaxis. Some of the patients who were experiencing a severe post-injection reaction received treatment as if they were experiencing an anaphylactic reaction, including treatment with epinephrine, steroids, antihistamines, and oxygen.

In 19 clinical trials of intramuscular testosterone, at various doses and dose regimens, in approximately 3600 subjects, there were 9 reported events of POME and 2 reports of anaphylaxis. This translates to an overall POME incidence rate of 4.6 cases per 10,000 injections, or 21.3 cases per 10,000 person-years; and an overall anaphylaxis incidence rate of 0.9 cases per 10,000 injections, or 4.7 cases per 10,000 person-years. In approximately 8 years of postmarketing experience with intramuscular testosterone undecanoate outside the United States, mostly at a dose of 1000 mg (4 mL) per injection, we identified 137 cases of severe POME or anaphylaxis. An additional 19 months of postmarketing experience showed no apparent change in the severity or frequency of reports. Although some of the events have been reported as serious, with hospitalization or emergency room visits, no case has led to death or permanent disability.

While there have also been rare reports of severe POME and anaphylaxis for testosterone enanthate and testosterone cypionate injections, the totality of reports in FDA's voluntary adverse event reporting system (FAERS) is 33 cases over a 44 year period for all approved T injections combined.

Based on the occurrence of rare but serious POME and anaphylaxis events for intramuscular testosterone enanthate, we required the Sponsor to submit a comprehensive Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). We also required the product labeling to include a Boxed Warning as well as a restricted new indication. In order to receive the product, health care providers will need to be specially certified. Product will only be distributed to certified heath care settings and certified health care providers. Health care providers will be trained in proper administration of the product. Health care providers will attest to their awareness of the risk of serious POME and anaphylaxis, their ability to manage the rare potential severe post-injection event, and their willingness to keep the patient under observation in the health care facility for 30 minutes. Patients will be thoroughly informed of the potential risk of serious POME and anaphylaxis. The Sponsor will manage this program on a continuous basis and will conduct periodic assessments to assure its effective functioning. The Sponsor will be vigilant to reports of

serious POME and anaphylaxis, will investigate them thoroughly, and will report them promptly.

I am convinced that the new Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) mitigates the potential adverse consequences of the rare serious POME and anaphylaxis reactions such that the benefit of Aveed now outweighs its potential risks in the restricted target population. I recommend that this application be **Approved**.

1.2 Sources of Clinical Data

1.2.1 Clinical Trial Data

The clinical trials of testosterone undecanoate injection consisted of a single U.S. Phase 3 Hypogonadism study (Study IP157-001), six European Phase 1, Phase 2 and Phase 3 Hyypogonadism studies, 6 European Male Contraception studies, and 6 International Postmarketing studies, including:

U.S. Hypogonadism Study (N=524)

- IP157-001 Parts A, B, C and C2*

(*A total of 153 subjects participated in the U.S. Study IP157-001 Parts C and C2 which employed the to-be-marketed 750 mg Loading regimen)

European Hypogonadism Studies (N=201)

- JPH01495, European hypogonadism, 1 dose, n=14
- JPH04995, European hypogonadism, multiple doses, n=14
- ME98096, European hypogonadism, multiple doses, n=26
- ME97029, European hypogonadism, multiple doses, n=36
- 306605, European hypogonadism, multiple doses, n=96
- 303934, Finland andropause (prematurely terminated), 1 dose, n=15

European Male Contraception Studies (N=447)

- 97028, Germany male contraception, 4 doses, n=28
- 97173, Italy, multiple doses, n=24
- 98016, Germany, 4 doses, n=14
- 99015, Germany, 4 doses, n=42
- 42306, 6 countries, 4 doses, n=298
- 303923, Italy, 4-6 doses, n=40

International Postmarketing Studies (N=2424)

- AWB0105, Germany, 4 doses, n=869
- 39732 (NE0601 IPASS), 18 countries, 4 doses, n=1411
- 14329 (Czech NEO), Czech Republic, multiple doses, n=23
- NB02, Germany (paraplegia), 2 doses, n=20
- TG09, Germany (obesity), 4 doses, n=29
- 14853, Prematurely terminated (older men), multiple doses, n= 3

1.2.2 Postmarketing Safety Update Reports

Additional clinical data for this application come from voluntarily submitted adverse event reports from 9.5 years of worldwide postmarketing experience with testosterone undecanoate injection outside of the United States.

The original NDA and three Complete Responses have included a total of eleven (11) Bayer/Schering Periodic Safety Update Reports (PSURs) from approximately 9 years of worldwide postmarketing use (specifically from November 25, 2003 through November 24, 2012), as well as an Addendum covering the period until May 24, 2013. Bayer-Schering is the Sponsor of TU outside the US.

1.2.3 Risk Evaluation and Mitigation Strategy (REMS)

The current submission contains an extensive REMS, which includes Elements to Assure Safe Use (ETASU) and a number of documents related to the structure and functioning of the Aveed REMS Program, including: the REMS Document, REMS Supporting Document, Health Care Provider Enrollment Form, Health Care Setting Enrollment Form, Health Care Provider Education Program, Health Care Setting Education Program, Health Care Provider Webpage, Patient Counseling Tool and Aveed REMS Program Introduction Piece.

2. Background

2.1 DESCRIPTION OF PRODUCT

Aveed contains testosterone undecanoate, an ester of testosterone. Although the esterified testosterone (T undecanoate) is itself detected in the blood following injection, the pharmacologically active androgen, testosterone, is formed by esterase cleavage of the undecanoate ester side chain. Aveed is formulated as a clear, yellowish, sterile, oily solution for intramuscular injection. It is supplied in single use vials, as 750mg testosterone undecanoate in 3mL solution. In addition to testosterone undecanoate, the product also contains refined castor oil (885mg) and benzyl benzoate (1500mg).

Aveed is intended for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

2.2 REGULATORY HISTORY

On August 24, 2007, the **original NDA** was submitted.

On June 27, 2008, the application received an ***Approvable*** action based upon *Clinical* and *Chemistry* deficiencies.

The original ***Clinical*** deficiency centered on immediate post-injection reactions. The etiology of these was believed to be pulmonary oil microembolism (POME) and/or anaphylaxis. While immediate post-injection reactions were reported in just 2 clinical trial patients in the original NDA, such events were reported in 66 patients in the postmarketing period outside of the United States. In the Approvable letter, the Sponsor was asked to submit additional

information to further assess and to mitigate the risk of these reactions. In this regard, the letter spelled out 3 specific requests for Clinical information.

1. *Detailed safety information from clinical studies to determine the incidence of serious post-injection POME and allergic reactions (in clinical studies).*

2. *Information from clinical investigations intended to characterize the nature and etiology of the anaphylaxis-like events with testosterone undecanoate injection.*

3. *A plan to minimize the risks associated with the clinical use of the product, namely, to reduce incidence and/or severity of the serious POME and anaphylaxis-like adverse events.*

The ***Chemistry*** deficiency came from Drug Master File (DMF) # (b) (4) The DMF deficiencies were related to the assessment of sterility of the drug product and were conveyed to the DMF holder in a regulatory letter dated June 25, 2008. The Approvable letter stated that these DMF deficiencies must be satisfactorily resolved prior to application approval. The reader is referred to Section 3 of my previous CDTL memos for details of the Chemistry deficiency and the means by which it was ultimately resolved.

On March 2, 2009, the Sponsor submitted the **first Complete Response**.

In this submission, the Sponsor reported 1 serious POME case and no systemic allergic reactions amongst 2,834 clinical trial subjects. The Sponsor thereby proposed an incidence of 1 serious POME in 2834 subjects, or 3.53 serious events per 10,000 subjects, or 0.035%. For systemic allergic reactions, the Sponsor proposed an incidence of 0% in clinical trials. The Division identified several other cases that may have reflected POME or anaphylaxis, although the data for those cases was too sparse to allow for definitive conclusions. The Division further identified a total of 116 post-injection reactions (POME and anaphylaxis) in the post-marketing period outside the U.S., many of which were severe events.

In addition, the Sponsor submitted a Risk Evaluation and Mitigation Strategy (REMS). The proposed REMS proposal included a Patient Package Insert (PPI), a Dear Health Care Professional (HCP) letter, and a Video for HCPs in regard to proper intramuscular injection technique (notably, slow and deep intramuscular injection with care taken to avoid intravascular injection). The Sponsor also submitted a proposal for two Phase 4 studies.

While the Sponsor had provided the information requested for the Complete Response, as well as a risk management plan, the Division remained uncomfortable with the occurrence of severe post-injection reactions.

It should be noted that the ***Chemistry*** deficiency in the original NDA had been satisfactorily resolved.

Therefore, on December 2, 2009, the application received a **Complete Response** action based upon a remaining ***Clinical*** deficiency. The Division expressed continuing safety concerns regarding reports of serious, immediate, life-threatening post-injection reactions and their impact on the risk/benefit profile. In addition, the proposed REMS was not considered adequate to assure that the benefits outweighed the risks associated with the use of testosterone undecanoate. The Division identified 2 potential remedial actions:

- Identify which components of the drug product may be contributing to the immediate post-injection reactions, and reformulate the product; or
- Identify a population of adult males who require testosterone replacement therapy (TRT) and in whom the additional potential risks associated with the use of TU injection as currently formulated would be acceptable.

On May 24, 2010, the Division met with Sponsor in a Type A meeting to discuss a potential path forward for the application. The Sponsor proposed a narrowed target population with a restricted distribution program under a REMS with ETASU. In response, the Division stated that a restricted distribution program under a REMS with ETASU might be a possible pathway forward in this situation.

On June 27, 2011, the Division met with Sponsor in Type C meeting. At that time, the Division recommended that the Sponsor submit another CR and the application would likely be discussed at an Advisory Committee Meeting.

On November 29, 2012, the **second Complete Response** was submitted. The submission contained additional information intended to better quantify the rate of serious POME and anaphylaxis cases as well as a revised REMS. On April 18, 2013, an AC Meeting was held to discuss the application. The AC was split as to the safety of the product (9 yes; 9 no) but was fairly unanimous (17:1) that the proposed risk mitigation strategy and product labeling needed improvement. Therefore, on May 29, 2013, the application again received a Complete Response action based upon inadequate risk mitigation. The Complete Response letter outlined in detail a REMS with ETASU that would be appropriate to ensure safe use of Aveed and also informed the Sponsor of the need for a restricted indication.

On August 29, 2013, the third Complete Response was submitted.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Guodong Fang, stated in his final review dated February 21, 2014:

> *"Recommendation on Regulatory Action: In the opinion of this Clinical Reviewer, from a clinical perspective, the evidence presented in the original submission and three re-submissions was adequate to support the effectiveness of this product. In regard to safety, the risk related to immediate post-injection reactions, including serious pulmonary oil microembolism (POME) and anaphylaxis has been the major safety concern. In the current re-submission, the Sponsor agreed to a restricted indication and proposed a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), including restricted distribution to prescribers who are aware of the risk, who explain the risk to patients, and who observe patients in their offices for 30 minutes after each dose. In addition, the proposed REMS includes a Patient Counseling Tool based on the Medication Guide that will completely inform the patient of the risk. Therefore, with this program, this reviewer believes that the major safety concern has been put under control and is resolved for use of Aveed in the proposed population with restricted distribution and proper management in certified*

*clinical health care settings. Therefore, this reviewer recommends an **Approval** action for this application.*

In regard to the risk/benefit profile, the medical officer concluded:

"During the last review cycle, the Clinical Review Team concluded that the postmarketing safety reports of severe post-injection reactions, including serious pulmonary oil microembolism (POME) and anaphylaxis, was a major unresolved safety issue.

After the Advisory Committee Meeting on April 19, 2013 and the Complete Response (CR) action from the Division on May 29, 2013, the Sponsor made additional efforts and resubmitted this NDA with an ETASU-based REMS designed to manage the risk of severe post-injection adverse reactions. The REMS includes measures to mitigate the risk of severe post-injection reactions, such as informing the patient of the risk, insuring the prescriber is aware of the risk, and insuring patients are observed in the office for 30 minutes after each dose. Only certified prescribers may receive Aveed for administration to patients. After careful review, this Clinical reviewer concludes that the REMS with ETASU acceptably ensures safe and effective use of the product in the indicated population.

In addition, at the Agency's request, the Sponsor agreed to include a "Black Box Warning" in the proposed labeling as well as to restrict the indicated population.

With these measures in mind, this Clinical reviewer concludes that the major risk of the product has been brought under control and that the benefits of the product outweigh the risks in the proposed population, under conditions of restricted distribution, with in-office observation for 30 minutes after each injection to allow for appropriate medical management in the event of serious POME or anaphylaxis."

CDTL Comment: I concur with Dr. Fang's overall conclusion and recommendation.

3. CMC/Device

For this cycle, in their final review, dated February 3, 2014, the CMC review team (Yichun Sun and Moo Jhong Rhee) concluded that the NDA is not recommended for Approval until the Office of Compliance makes an overall Acceptable recommendation. The CMC review team required the outcomes of an ongoing inspection of the drug substance manufacturing site (b) (4)

On February 24, 2014, the Office of Compliance entered an overall Acceptable recommendation to the EES system.

On February 25, 2014, in a final review, the CMC review team noted that the Office of Compliance provided an overall "Acceptable" recommendation. Therefore, the application is now recommended for Approval from the ONDQA perspective.

Otherwise, the CMC review team notes that the for this re-submission, the two DMFs ([(b) (4)] and [(b) (4)]) were adequate as of August 5, 2013, and there have been no further amendments for the DMFs, and therefore the two DMFs are still deemed adequate. In addition, the submitted information on labels and labeling are satisfactory.

4. Nonclinical Pharmacology/Toxicology

For this review cycle, in their final review, dated October 15, 2013, the nonclinical review team (Eric Andreason and Lynnda Reid) concluded that the Sponsor's nonclinical program, references from the literature, and general knowledge of testosterone provided reasonable assurance of the safety of testosterone undecanoate (TU) in hypogonadal men. In their review, the nonclinical review team provided recommendations for labeling. The current re-submission contained no new nonclinical information.

Previously, the nonclinical reviewers noted that the Sponsor had conducted a local toxicity that demonstrated only non-specific tissue injury at the site of injection.

In regard to previous PharmTox review issues, there is one issue of potential clinical relevance: the potential for benzyl benzoate to act as a toxin.

> In their original Pharmacology/Toxicology review, Drs. Andreason and Reid provided results from a local tolerance study of Nebido (containing intramuscular testosterone undecanoate, refined castor oil, and benzyl benzoate) in pigs. This study is reviewed on page 47 of the final PharmTox review, dated April 18, 2008. It is stated that this study was reviewed by Dr. Leslie McKinney. The results of this study, wherein pigs were injected intramuscularly with low and high volumes of the drug product, or with vehicle alone, showed areas of gross hemorrhage and necrosis at the injection sites, with necrotic tissue, inflammation and multinucleated giant cells on histopathology. All groups showed similar effects, including the vehicle alone group. The reviewer concluded that these observations are likely due to non-specific tissue injury, and that there is no direct evidence that either of the excipients, or testosterone undecanoate itself, were directly toxic to tissues. However, Dr. McKinney noted that benzyl benzoate is itself a toxin, as shown by its use in the treatment of scabies to kill the house mite that causes scabies. The review states: "*Whether it (benzyl benzoate) could directly activate macrophages, which would explain the presence of giant cells at the injection site, has not been established, but has been observed for other benzoates in vitro (Choi et al., Arch Pharm Res: 28[1]:49-54 [2005])*".
>
> The reader should also be aware that AVEED contains 1500mg of benzyl benzoate per vial, a fairly large amount. I have discussed this with the primary pharmacology/toxicology reviewer, Dr. Andreasen, who has indicated that he could find no approved product containing more than 750mg of benzyl benzoate. Benzyl benzoate is the condensation product of benzyl alcohol and benzoic acid. In a final report on the safety of benzoates (benzyl alcohol, benzoic acid, and sodium benzoate) in cosmetics, the U.S. Cosmetic Ingredient Expert Panel noted that benzyl alcohol and benzoic acid can produce nonimmunologic contact urticaria and non-immunologic immediate contact reactions (Int

J. Toxicology 2001; 20 Suppl 3:23-50). The Panel stated that such reactions were not a concern at concentrations up to 5% topically; that is, when bodily exposure is limited. Nonetheless, the panel stated that the clinical risks of these reactions should be considered by manufacturers when assessing topical use of products containing benzyl benzoate in infants and children; and that an inhalational route for these products could not yet be considered safe. Benzyl benzoate appears to have played a role in at least one case of severe post-injection reactions reported in the postmarketing period outside the United States. In that case, a young man experienced an anaphylactic reaction to testosterone undecanoate injection and subsequent skin testing revealed a positive reaction to the benzyl benzoate component only.

5. Clinical Pharmacology/Biopharmaceutics

For this review cycle, in their final review, dated February 20, 2014, the Clinical Pharmacology review team (Hyunjin Kim and Myong-Jin Kim) found the application acceptable for approval provided that an agreement was reached on all outstanding labeling issues. All labeling issues have been resolved through labeling discussions with Sponsor. There were no new clinical pharmacology data submitted in this resubmission.

In regard to prior Clinical Pharmacology review issues:

Excessive testosterone exposure was noted in a single patient who weighed <65 kg. This led to a potential concern that the increased exposure may be demonstrated in patients with lower body weight/lower body mass index. To resolve this issue, the ClinPharm review team considered several options for labeling, including a possible new Warning/Precaution. Ultimately, it was decided to create a new section within Section 12.3 (Pharmacokinetics) entitled "*Effect of Body Weight and Body Mass Index (BMI)*". This new section describes in detail the effect of body weight on exposure.

Testosterone undecanoate (TU) concentrations were observed in the blood in patients administered Aveed. While TU is generally converted to T, serum TU concentrations were clearly identified in all regimens tested. The concentration-time profile showed that T_{max} was approximately 4 hours for TU and serum TU concentrations were generally short-lived. The reader should also be aware that while TU may be found in the blood, nonclinical studies have shown that TU itself has little potential for clinical androgenic activity. The ability of TU to bind to the human androgen receptor was assessed and the results suggest that TU does not have significant androgenic activity since its relative binding affinity was only 1.3% of testosterone. Nonetheless, Section 12.3 (Pharmacokinetics) describes the maximum TU concentrations observed in patients on Day 4 after dosing as well as the almost undetectable TU concentrations observed on Day 42 after dosing.

6. Clinical Microbiology

On April 29, 2009, the Clinical Microbiology review team (Vinayak Pawar and David Hussong) recommended approval of the NDA. Upon review of amendment 9-11 to DMF

(b) (4) (referred for the drug product), the original Micro recommendation for approval of the NDA remain unchanged, as there was no new information which would alter the conclusions based upon review of data from the previous DMF (b) (4) submissions. For this review cycle, there was no new Micro information and no new Micro review.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

For efficacy, the NDA is supported by a single, two-part, phase 3 safety and efficacy study, referred to as Study IP157-001 - Parts C and A. Part C evaluated the 750 mg Loading regimen (n = 117), which is the to-be-marketed dose regimen, while Part A evaluated 750 mg (n=102) or 1000 mg (n=97) given every 12 weeks. The primary endpoints in this study were average and maximum serum testosterone (T) concentrations.

Results from five (6) other European Hypogonadism studies and their extensions (including Study JPH01495, Study JPH04995, Study ME98096, Study ME97029, Study 306605 and Study 303934) were provided but were not reviewed in depth for efficacy because they employed dose regimens that were not sought for marketing. In addition, these older studies employed testosterone assay methods (radioimmunoassay or electrochemoluminescence immunoassay) that were regarded by Clinical Pharmacology as being not as accurate as the method used in Study IP157-001.

(b) (4) in a teleconference dated January 15, 2008, the Sponsor requested that the Division consider for approval just the TU 750 mg Loading regimen, as studied in Study IP157-001 Part C. Due to this change, data from Study IP157-001 Part C were used as the source of steady state PK. However, data from Study IP157-001 Part A was used as the source of first-dose PK because Part C did not evaluate first-dose PK. Part A also served as the primary source of data on serum TU and serum dihydrotestosterone undecanoate (DHTU) concentrations because these analytes were not measured in Study IP157-001 Part C.

7.2 DEMOGRAPHICS

The main diagnostic criteria for inclusion in Study IP157-001 were men at least 18 years of age with morning screening serum testosterone concentration < 300 ng/dL. Critical exclusion criteria included: 1) American Urological Association Symptoms Score ≥ 15 points, 2)

Prostate symptoms or induration of the prostate (or breast) suspicious for cancer, 3) Serum prostate specific antigen level ≥ 4 ng/mL, 4) Hyperplasia of the prostate, defined as prostate size ≥ 25 cm^3 on transrectal ultrasononography, 5) Past or present history of liver tumors, acute or chronic liver disease, or serum liver function tests exceeding 1.5 times upper limit of normal, 6) History of deep vein thrombosis (DVT) in the last 5 years, 7) Any history of cerebrovascular accident, 8) Severe acne, 9) Serious psychiatric disease or other uncontrolled medical illness, 10) Significant baseline hypertension (systolic BP > 160 mmHg and diastolic > 95 mm Hg), 11) Coronary artery disease not stabilized by therapy, and 12) Insulin dependent diabetes mellitus, or uncontrolled non-insulin dependent diabetes mellitus.

In brief, the demographics of the study population in Part C (n=130) were as follows:

In terms of race, the majority of subjects were White (76%), 12.3% were Black, 10.8 % were Hispanic, and 2.3% were "Other". The mean age was 54 years ± 0.9 years. The median age was 55 years. The minimum and maximum ages of subjects in the trial were 24 years and 75 years, respectively. Of the total, 23% (30/130) were between ages 40 - 50 years, 38% (50/130) were between ages 50 - 60 years, and 25% (33/130) were 60 - 70 years. The mean weight of subjects was 71 kg ± 14 kg. The median weight was 101 kg. The mean body mass index was 32 kg/m^2. Almost 60% of subjects had a body mass index over 30 kg/m^2. The average total testosterone concentration at screening was 214 ng/dL.

7.3 DISPOSITION OF SUBJECTS

For Part C, a total of 130 patients were enrolled at a total of 31 U.S. clinical sites. Of the 130 patients enrolled, 116 (89%) completed Stage 1 of Part C; that is, they completed through the 4^{th} injection visit. Of the 14 subjects who prematurely discontinued, the most common reason for premature discontinuation was adverse event (3.8%, or 5/130). Of the 5 who discontinued due to an adverse event, the adverse event was judged by the investigator to be related to treatment in 4 patients. The events in these 4 patients included: mood swings, acne, deep vein thrombosis, and estradiol increased. The fifth patients suffered a myocardial infarction, judged by the investigator as being not related to study medication. Other reasons for premature discontinuation included: patient non-compliance (3 subjects), withdrawal of patient consent (1 subject), loss to follow-up (2 subjects), and "other" reasons (3 subjects). The Sponsor notes that despite the requirement for frequent blood sampling in this study, persistence on drug therapy was high.

Of note, two subjects were discontinued from the study for weighing less than 65 kg, but only after they had been enrolled.

There were 4 pre-defined criteria in the protocol for subject discontinuation. These were: hemoglobin >21 gm/dL, PSA > 10 ng/mL, PSA > 4ng/mL but ≤ 10 ng/mL unless prostate cancer was ruled out by new biopsy, and uncontrolled hypertension, defined as systolic blood pressure ≥ 160 and diastolic BP ≥ 95 mm Hg. There were no patients who terminated from the study due to any of these 4 criteria.

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

The primary efficacy variable was the percentage of patients with average T concentration at steady state within the normal range (above 300 ng/dL but below 1000 ng/dL). Testosterone undecanoate 750mg was given at baseline, week 4, and every 10 weeks thereafter. Steady state pharmacokinetic sampling occurred during the 3rd injection interval. This is the currently acceptable primary efficacy endpoint for the proposed indication.

A total of 117 patients were included in the PK population. The majority of patients in the PK population had complete data for most efficacy outcomes. The Sponsor's analysis presented descriptive statistics (mean, standard errors, etc) for all patients with non-missing values. A point estimate was provided for the number (%) of subjects meeting the C_{avg} threshold, as were the 95% confidence intervals about the point estimate. The protocol stated that in order to reject the null hypothesis (TU 750mg Loading regimen does not provide adequate T replacement) in favor of the alternate hypothesis (TU 750mg Loading regimen does provide adequate T replacement), the percentage of responders, defined as C_{avg} within the normal range (300-1000ng/dl), must be at least 75%, with the lower bound of the two-sided confidence interval not lower than 65%.

The protocol also stipulated that testosterone concentrations should not be excessively high outside the normal range; specifically, $\leq$ 1500 ng/dL in $\geq$ 85% of patients, 1800 – 2500 ng/dL in $\leq$ 5% of patients, and > 2500 ng/dL in no patients. All 3 criteria must be met to reject the null hypothesis (TU 750mg Loading regimen does result in excessively high serum T) in favor of the alternative hypothesis (TU 750mg Loading regimen does not result in excessively high serum T).

In addition, the following secondary endpoints were evaluated:

1. Other pharmacokinetic assessments of testosterone, including concentrations below the normal range (<300 ng/dL).
2. Other hormone concentrations, including free T, dihydrotestosterone (DHT), sex hormone binding globulin, estradiol (E_2) and the ratios of these hormones over time.
3. Exploratory clinical markers of testosterone replacement, including the Male Patient Global Assessment (M-PGA).
4. Body weight and BMI.
5. Correlations of T concentrations with clinical outcomes.
6. The impact of T concentrations on erythropoiesis and lipid markers.

7.4.1.1 Primary Efficacy Analysis

The mean pharmacokinetic data indicated that the serum testosterone C_{trough} values were similar at end of 2nd, 3rd, and 4th injection interval, as shown in *Figure 1*. A comparison of serum total T concentration at several time points post-injection during the 3rd and 4th injection intervals demonstrated similar concentration-time profiles (*Figure 2*). Taken together, these data indicate that steady state was achieved during the 3rd injection interval in Part C, and that this was an appropriate timepoint for assessment of the primary endpoint.

Figure 1: Mean (±SD) trough serum total T concentrations at each injection visit from pre-treatment through 5th injection – Steady state PK population, Study IP157-001 Part C

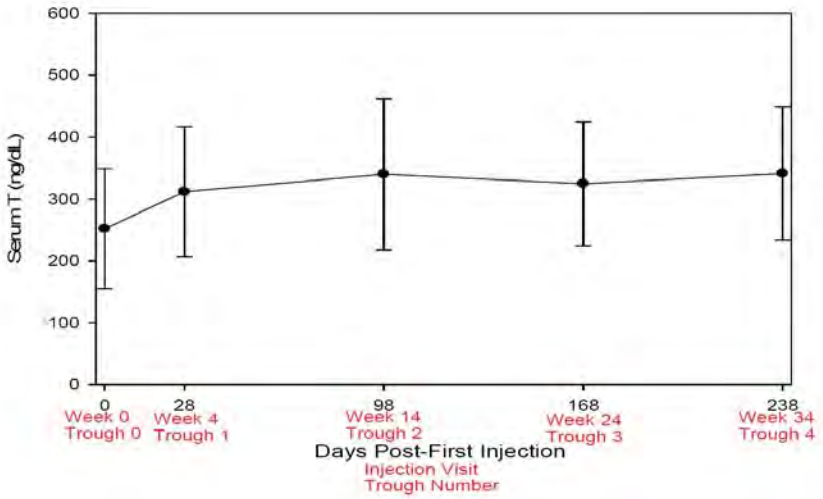
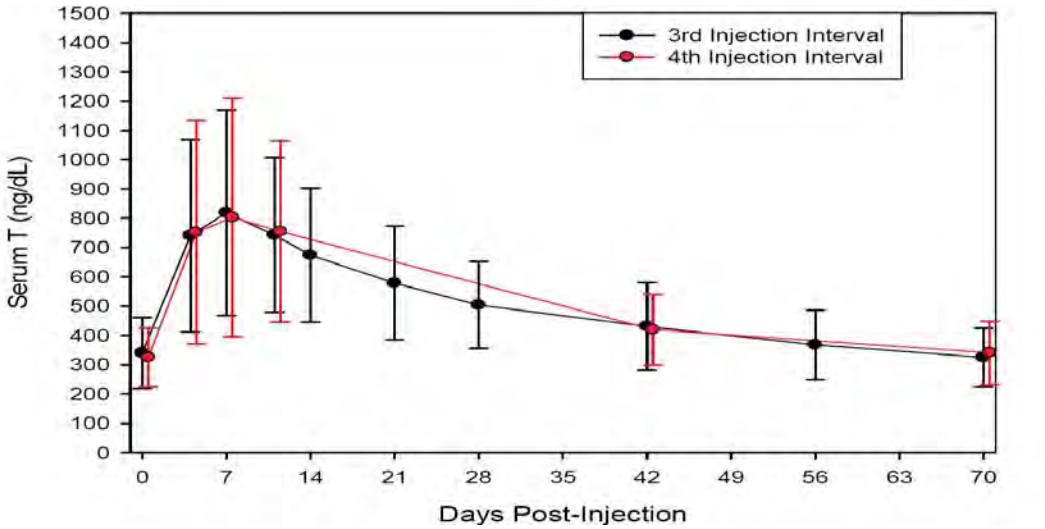


Figure 2: Comparison of serum total T concentrations between the 3rd and 4th injection intervals – Steady state PK population, Study IP157-001 Part C



Tables 1, 2 and 3 summarize the pharmacokinetic parameters of serum total T from the 3rd injection interval. The primary endpoint was $C_{average}$.

Table 1. Serum total T pharmacokinetic parameters from the 3rd injection interval, TU 750mg LOADING regimen, from Study IP157-001 Part C

PK parameter	Mean (n=117)	Standard deviation
C_{avg} (ng/dL)	495	141
C_{max} (ng/dL)	891	345
T_{max} (days)	7 (median)	4 – 42 (range)

Table 2: PK parameters of serum total T (ng/dL) following the 3rd injection interval of TU 750 mg LOADING regimen - PK population, Study IP157-001 Part C

TU Dose	Pharmacokinetic Parameter	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV (%)	Geometric Mean
TU 750 mg LOADING	$AUC_{(0-70)}$ (days*ng/dl)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
	C_{Trough} (Day 70)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
	C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
	Dose-normalized C_{max}(ng/dL)[1]	117	1.2	0.46	0.4	1.1	2.3	38.8	1.1
	T_{Last} (days)	117	70.0	0.00	70.0	70.0	70.0	0.0	70.0
	T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
	Dose-normalized $AUC_{(0-70)}$ (days*ng/dl)[1]	117	46.2	13.20	18.3	44.5	93.4	28.6	44.4
	$C_{avg, 0-70}$ (ng/dL)[2]	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

Reference: Section 14.2 Table 9.2.1.1.1
CV = Coefficient of Variation
[1] Statistics for the dose normalized AUC were derived by dividing the mean of the original parameter ($AUC_{(0-70)}$) by the dose amount (750 mg). Thus, no measures of variability, geometric mean, or CV are presented for the dose normalized AUC.
[2] C_{avg} derived as $AUC_{(0-70)}$/70 days

Table 3: Serum total T concentrations (ng/dL) over 70 days (10 weeks) following the 3rd injection of TU 750 mg LOADING regimen - PK population, Study IP157-001 Part C

Treatment Group	Days Post-Injection	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV%	Geometric Mean
TU 750 mg LOADING	0 (Pre-Injection)	117	339.5	122.69	141.4	303.0	754.1	36.1	319.8
	4	111	730.1	325.36	304.6	656.4	1715.0	44.6	662.9
	7	111	816.9	352.15	276.4	737.6	1758.5	43.1	747.5
	11	107	750.1	280.64	245.6	740.9	1757.0	37.4	697.9
	14	114	661.6	237.55	230.9	610.8	1352.3	35.9	619.2
	21	115	573.5	197.15	182.7	558.6	1350.4	34.4	541.3
	28	111	501.6	149.92	190.9	481.4	947.0	29.9	479.5
	42	109	432.3	152.16	171.3	399.8	1161.2	35.2	409.5
	56	115	367.0	120.67	144.5	349.8	780.8	32.9	348.7
	70[1]	116	323.8	99.51	138.2	317.2	611.1	30.7	309.2

Reference: Section 14.2 Table 9.2.1.2.1
[1] Note: As per the statistical analysis plan, for derivation of the PK parameters, if the concentration at the end (Day 70) of the 70-day dosing interval is missing, then the AUC was derived using λz as derived by curve-stripping. There was 1 patient who was missing a Day 70 concentration value; this table presents the data prior to the data imputation of Day 70 for this patient. However, the analysis for Table 25 was performed using the imputed data for the last value for that patient, and thus the C_{trough} value from that table will not match the Day 70 value from this table.

One patient was excluded from the PK analysis due to protocol violation. This was Patient 002-7022, who was taking concomitant DHEA, an androgenic steroid hormone prohibited in this study.

Figures 3 and 4 show the mean and individual concentration-time profiles for serum testosterone, respectively, following the 3rd injection interval.

Figure 3: Mean (±SD) serum total T concentrations following the 3rd injection interval of TU 750 mg LOADING regimen, from Study IP157-001 Part C

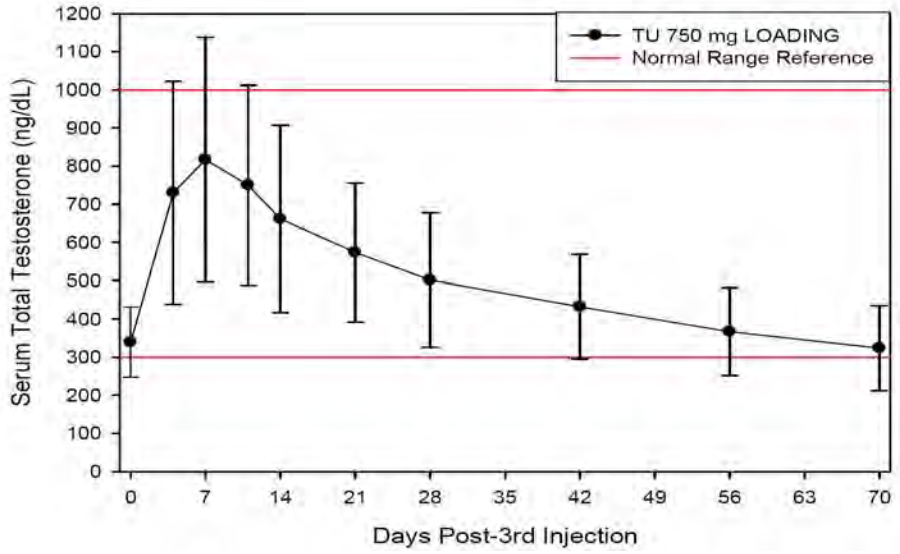
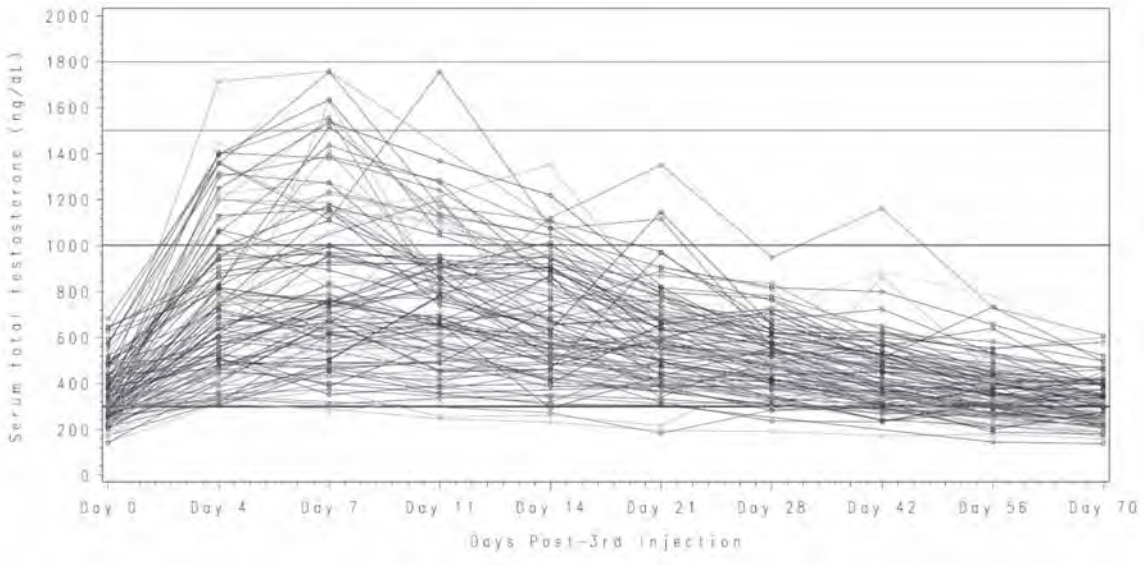


Figure 4: Composite of individual serum total T concentration following the 3rd injection of the TU 750 mg LOADING regimen – PK population, Study IP157-001 Part C



The primary efficacy endpoint in this study was the percentage of responders defined as C_{avg} within the normal range (300 – 1000 ng/dL). To meet the primary efficacy criterion, the point estimate for the pre-determined primary endpoint was set as at least 75% and the lower bound of the two-sided 95% confidence interval was set as not lower than 65%.

Ninety-four percent of patients (110 of 117) had serum total T C_{avg} within the 300 – 1000 ng/dL range. The 95% confidence interval around this point estimate was 89.6 - 98.5. Of the 7 patients who did not meet this criterion, 6 failed due to $C_{average}$ below 300ng/dL and one failed due to a $C_{average}$ above 1000ng/dL.

Therefore, the data from Part C show that the primary efficacy objective was achieved.

7.4.1.2 Secondary Efficacy Analysis

C_{max} was an important secondary efficacy endpoint in Part C. To meet the C_{max} efficacy criterion, the criteria shown in *Table 4* were pre-defined:

Table 4: Decision criteria for Cmax

Criteria for Serum Total Testosterone Maximum Concentration Observed	Criteria for Success	Not Meeting the Criteria for Success
≤ 1500 ng/dL	≥ 85% of Patients	< 85% of Patients
1800 - < 2500 ng/dL	≤ 5% of Patients	> 5% of Patients
≥ 2500 ng/dL	No Patients	At least 1 patient
All 3 criteria must be met in order to reject the null hypothesis in favor of the alternative hypothesis. If at least one of the 3 criteria is not met, the null hypothesis cannot be rejected. The time point for assessment of this secondary outcome is the post-3rd injection period (Weeks 14 - 24).		

Based upon pre-defined eligibility criteria, the Sponsor excluded from the PK analysis those patients who weighed less than 65kg. One patient (a protocol violation) fell into this category in Part C (Patient 031-7021). This patient did experience a serum testosterone concentration above 2500 ng/dL during the 3rd injection interval. Otherwise, only nine of the 117 patients (7.7%) had C_{max} > 1500 ng/dL and no patient had $C_{max} \geq$ 1800 ng/dL.

In summary, the data show that the C_{max} efficacy objective was achieved in Part C in men weighing more than 65 kg.

In addition to the increase in serum total T concentration, the serum concentrations of free T and known downstream metabolites, dihydrotestosterone and estradiol, were also increased. The increases in serum DHT and E_2 were expected. Average DHT concentrations tended to remain within the lower end of the normal range, while average E_2 concentrations tended to remain in the middle of the normal range. TU administration did not affect concentrations of sex hormone binding globulin (SHBG). With SHBG and albumin concentrations unchanged, the increase in free T concentration was also expected. The concentration versus time profiles for free T, DHT and E_2 generally paralleled the T concentration-time profile. DHT:T and E_2:T ratios were unchanged. The reader is referred to the original and subsequent medical officer's primary reviews and to the Clinical Pharmacology reviews for additional details, tables and figures for these variables.

In regard to other secondary endpoints:

- Average values of hemoglobin and hematocrit increased slightly from pre-treatment, as average T concentrations increased. The average increases in these markers of erythropoiesis were small and average values remained within the normal range.

- The improvement seen in "treatment satisfaction" appeared to correlate with higher T concentrations in some patients. Overall, 92% of patients expressed satisfaction with treatment.
- At Day 21 of the 3rd injection interval, > 80% of patients demonstrated improvements in each item of the M-PGA questionnaire.
- Changes in T concentrations were weakly inversely correlated with changes from baseline in body mass index (BMI) and weight. However, there were no notable changes in other body composition measures.

Statistician's Conclusion

For this cycle, in his final review dated February 4, 2014, the Biometrics Team Leader (Mahboob Sobhan) stated that no new efficacy data was submitted in this resubmission. Therefore, no statistical input was necessary.

In prior reviews, the Biometrics Team Leader (Mahboob Sobhan) had the following conclusions:

> For the review of the original NDA submission (review dated June 24, 2008): "*The results support the efficacy of Nebido TU 750 mg LOADING in the treatment of hypogonadism in adult male as indicated by the attainment of steady state by the 3rd injection. The intensive sampling for PK outcomes (Cavg and Cmax) also met FDA threshold for approvability and, therefore, can be extrapolated to represent PK outcomes under extended dosing beyond 3 injections.*"
>
> For the first Complete Response submission (review dated July 21, 2009): "*In our earlier statistical review, we concluded that testosterone undecanoate (TU) was efficacious in treating hypogonadism in adult males. There were no new efficacy data submitted for our review to further substantiate or change the efficacy data in the label. We have reviewed the new label and from a statistical perspective, our conclusions remain unchanged.*"
>
> For the second Complete Response: No new statistical analyses were conducted as part of the review of the second CR.

7.4.2 Overall Assessment of Efficacy

The TU 750mg Loading regimen was found to provide adequate replacement of testosterone in hypogonadal men weighing >65kg (as measured by testosterone $C_{average}$), while not providing excessive testosterone (as measured by testosterone $C_{maximum}$). The dosing regimen demonstrated a C_{avg} within the normal range and a C_{max} profile that did not exceed the approvability thresholds provided. Thus, the primary efficacy objectives of the Phase 3 study were met.

8. Safety

8.1 SAFETY FINDINGS

This Safety Introduction provides an overview of the contents and safety findings from the original NDA and each of the three subsequent Complete Response submissions.

Contents and Safety Findings From the Original NDA

The original NDA submission contained safety data from 6 studies, as follows:

1) The single U.S. pivotal Phase 3 study IP157-001, including Parts A, B and C.
   a. Part A included a total of **237** adult male subjects, enrolled in two dose arms: 750mg every 12 weeks (*n=120*) and 1000mg every 12 weeks (*n=117*)

   b. Part B included a total of **134** adult male subjects in two treatment groups: *112 patients* received an initial injection of TU 1000 mg, followed 8 weeks later by a loading injection of 1000 mg and then 1000 mg every 12 weeks thereafter, while *22 patients* received an initial injection of 1000 mg, followed 8 weeks later by a loading injection of 750 mg and then 750 mg every 10 weeks thereafter.

   c. Part C included a total of **117** adult male subjects enrolled in the 750mg Loading regimen, *the to-be-marketed dosage regimen*. The Sponsor also submitted safety data on another **36** adult male subjects taking the 750 Loading regimen in a longer-term extension study (referred to as Part C2)

2) Five, older, European, dose-finding trials comprising a total of **185** adult male subjects (Studies JPH01495, JPH04995, ME98096, ME97029 and 306605).

When combined, **a total of 709 adult male hypogonadal subjects** contributed safety data from controlled studies to the original NDA.

The original NDA also contained six (6) Bayer/Schering Periodic Safety Update Reports (PSURs) from approximately 3.5 years of worldwide postmarketing use (specifically November 25, 2003 through June 30, 2007). Bayer-Schering is the Sponsor of TU outside the US. The 120-Day Safety Update to the original NDA contained a more recent postmarketing safety update report from Endo for the time period June 30, 2007 to October 12, 2007. Finally, the original NDA included a Summary Report entitled, "*Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism*" (report dated February 12, 2008).

In the opinion of the Clinical review team, the clinical trial safety data was consistent with an injectable androgen, except for the occurrence of immediate post-injection reactions in 2 patients. These 2 events were described as urge to cough with dyspnea, and a coughing fit, immediately following injection. The PSURs and Summary Report of Post-Injection Reactions raised concerns related to immediate post-injection respiratory and allergic-type adverse events. While there had been only 2 such events reported in 2 patients in clinical trials, the PSURs and Summary Report of Post-Injection Reactions included 66 postmarketing cases. The 66 postmarketing cases were marked by cough, shortness of breath, throat-related

symptoms (throat tickle, throat tightness, throat fullness, etc), flushing, allergic-type phenomenon (such as rash, pruritis, itching), tachycardia, palpitations, BP changes, and constitutional symptoms, such as headache, malaise, shivering, sweating, weakness and nausea.

Based largely on the occurrence of these post-injection reactions, the Division issued an Approvable letter for the original NDA.

Contents and Safety Findings from the First Complete Response

In the first Complete Response, the Sponsor provided safety data from an additional 11 clinical studies; 7 completed and 4 ongoing. The data was submitted as a new Summary Report, entitled, "*Incidence of Injection-Based Pulmonary Oil Reactions and Allergic Reactions from Clinical Studies of TU*" (report dated February 12, 2009). Final or interim study reports were provided for each of the 11 new studies. These 11 new studies comprised **a total of 2,125 additional subjects**. These studies were:

- AWB0105, Germany, 4 doses, n=870
- NE0601 (IPASS), 18 countries, 4 doses, n=763
- TG09, Germany (obesity), 4 doses, n=29
- NB02, Germany (paraplegia), 2 doses, n=19
- Czech NEO, Czechoslovakia, 4 doses, n=23
- 303934, Finland (andropause), 1 dose, n=15
- 97028, Germany, 4 doses, n=28
- 97173, Italy, 1 dose, n=24
- 99015, Germany, 4 doses, n=42
- 98016, Germany, 4 doses, n=14
- 42306, 6 countries, 4 doses, n=298

Therefore, for the first Complete Response, the overall clinical trial safety database was **2,834 subjects** in 17 trials.

The Sponsor also submitted two additional postmarketing safety updates (Bayer/Schering PSUR 7 and PSUR 8), bringing the total duration of postmarketing experience to approximately 5.5 years:

- A Bayer/Schering PSUR for the time period November 25, 2007 through November 24, 2008
- A Final Safety Update from Endo for the time period November 25, 2008 – August 29, 2009

To briefly summarize the Safety findings from the first Complete Response:

1) In regard to the incidence of post-injection reactions in clinical trials, the original NDA contained 2 such cases. The two original NDA clinical trial cases were:
   - Patient #184 in Study 306605. A 54 year old male received his 10th injection of testosterone undecanoate on 3 April 2006 and shortly (1 minute) after the injection, he "experienced urge to cough associated with respiratory distress". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study.

- Patient #050-7006 in Study IP157-001 Part C). A 53 year old white male received his 3rd injection on 12 July 2007 and experienced a "mild and not serious coughing fit lasting 10 minutes following the injection." The narrative describes the patient's cough as not productive, without wheezing and without difficulty breathing. No intervention was given and the patient continued on-treatment without subsequent coughing event.

The Sponsor detected no additional cases amongst the 2125 additional subjects. The Sponsor therefore counted 1 serious POME case and no systemic allergic reactions in the numerator. The denominator was totaled as 2,834 subjects. The Sponsor thereby proposed an incidence of 1 serious POME in 2834 subjects, or 3.53 serious events per 10,000 subjects, or 0.035%. For systemic allergic reactions, the Sponsor proposed an incidence of 0% in clinical trials.

The Clinical review team detected 6 additional potential cases of interest from clinical trials. However, information from these cases was too sparse to ascribe a specific etiology to the events, but nevertheless, they were all severe, immediate post-injection reactions. The Clinical review team believes that the former 3 events have a greater chance of being serious POME or systemic allergic reactions compared to the latter 3, but all 6 are notable. The former 3 cases are:

- Patient #11 in Study 97173 (convulsions)
- Patient #17 in Study 97173 (collapse),
- Patient #4 in Study JPH04995 (circulatory collapse)

If just these 3 cases were added to the numerator, this would result in an incidence of immediate post-injection reactions in clinical trials of 4 events in 2834 subjects (0.14%).

The latter three cases are:

- Patient #025-4187 in Study IP157-001 Part A (pre-syncope)
- Patient #26 in Study 97029 (syncope)
- Patient #35 in Study 97029 (circulatory collapse).

In summary, whether the clinical trials show 2, 5 or 8 incident cases is not as critical as the overall picture, especially coupled with the findings from postmarketing reports, which show the occurrence of severe and life-threatening immediate post-injection reactions.

2) In regard to the postmarketing Safety Updates submitted in the first Complete Response, the Clinical review detected 52 new cases of immediate post-injection reactions. Of these 52 cases, almost all were severe, and approximately 20 appeared to reflect anaphylaxis. The Clinical review team also expressed concern related to a case of full-blown, post-injection anaphylaxis in a 16 year old male.

Based on the totality of the safety data in the first Complete Response, especially in light of the occurrence of severe immediate post-injection reactions in the post-marketing period outside the United States, the Division issued a Complete Response action for the first Complete Response.

Contents and Safety Findings from the Second Complete Response

In the second Complete Response, the Sponsor provided safety data from one additional study, bringing the total to 18 clinical studies. The total number of clinical trial subjects included in the pool for analysis of adverse events of interest (POME and anaphylaxis) from this compilation of clinical trials was **3,556 subjects**.

In addition to this clinical trial experience, the second CR included the results of a detailed and extensive search of the Bayer/Schering postmarketing safety databases for cases of POME and anaphylaxis for testosterone undecanoate injection. FDA and Endo had agreed in advance on terms to be used in this search. According to the analysis conducted by Endo Pharmaceuticals internal assessors, this search identified a total of 307 post-injection reaction cases, including 228 cases of POME and 79 cases of anaphylaxis. A subsequent second analysis by "independent adjudicators" contracted by Endo Pharmaceuticals identified a total of 268 post-injection reaction cases, including 223 cases of POME and 45 cases of anaphylaxis. In compliance with FDA's request, the Sponsor included individual CIOMS reports in the second CR submission for all postmarketing adverse events of potential interest (e.g., POME and anaphylaxis).

The Sponsor also submitted three additional postmarketing safety updates (including Bayer/Schering PSUR 9 and PSUR 10 and a postmarketing update from Endo) in this second Complete Response, bringing the total duration of postmarketing experience to approximately 8.5 years:

- A Bayer/Schering PSUR for the time period November 25, 2009 through November 24, 2010
- A Bayer/Schering PSUR for the time period November 25, 2010 through November 24, 2011.
- A PSUR Addendum Report for the time period November 25, 2011 through April 30, 2012.

To briefly summarize the Safety findings from the second Complete Response:

1. In regard to the incidence of post-injection reactions in clinical trials, in an analysis of all cases adjudicated as POME or anaphylaxis among 3,556 subjects in 18 clinical trials,
   a. There was one (1) POME case among the 467 men who received 750 mg TU, and eight (8) POME cases among the 3089 men who received 1000 mg TU. Thus, for both doses combined, there were 9 POME cases among 3556 subjects, which translates to 4.6 cases per 10,000 injections, or 21.3 cases per 10,000 person-years.

   b. There were no reports of anaphylaxis among 467 men who received 750 mg TU. There were two (2) cases of anaphylaxis among 3089 men in the 1000 mg dose group. Thus, for both doses combined, the rate of anaphylaxis is 0.9 cases per 10,000 injections, or 4.7 cases per 10,000 person-years.

2. In regard to the postmarketing Safety Updates,

a. FDA reviewed case narratives for 330 potential cases of anaphylaxis for the entire postmarketing experience for testosterone undecanoate. From these, we identified a total of 53 and 76 cases of anaphylaxis, using strict and less restrictive anaphylaxis identification criteria, respectively.

b. FDA reviewed case narratives for 533 potential cases of POME. We identified a total of 170-191 cases of POME cases (the range is due to overlap with anaphylaxis cases identified using strict or less strict anaphylaxis identification criteria and thus, greater or fewer POME cases are tallied). Of these, we adjudicated 55-76 cases as severe POME.

Based on this safety information, as well as the advice provided to FDA by a joint meeting of the Reproductive Health and Risk Management Advisory Committees on April 18, 2013, DBRUP issued another CR action, this time requiring submission of a Risk Evaluation and Mitigation Strategy (REMS) focused on mitigating the risks associated with serious POME and anaphylaxis.

Contents and Safety Findings from the Third Complete Response

In this third Complete Response, the Sponsor submitted a detailed and extensive Risk Evaluation and Mitigation Strategy (REMS) including Elements to Assure Safe Use (ETASU). The REMS would assure that Aveed was only administered by certified prescribers who were aware of the risks of serious POME and anaphylaxis, who would share that risk information with potential patients, and who would observe the patients in the healthcare setting for at least 30 minutes after each injection.

In regard to new safety information, the third Complete Response included one, small, postmarketing clinical study conducted in 2004 in which 40 subjects were administered intramuscular TU and the progestin noresthisterone enanthate for the purposes of investigating this combination as a potential male contraceptive. In addition, the submission also included a Safety Update for another 19 months of worldwide postmarketing experience with intramuscular testosterone undecanoate.

The safety information in this submission did not yield any qualitatively new information. The data is discussed in more detail in the sections that follow.

> *The routine safety data presented in the next two sections (Section 8.1.1 [Deaths, Serious Adverse Events and Discontinuations due to Adverse Events] and Section 8.1.2 [Other Adverse Events, including Overall Adverse Events and Adverse Events of Interest]) come from the pivotal U.S. trial IP157-001 Parts C and A. The postmarketing safety data (from outside the U.S.) is described in Section 8.1.3 (Postmarketing Safety Findings).*

8.1.1 Deaths and Serious Adverse Events

Deaths, Serious Adverse Events, and Discontinuations due to AEs in Study IP157-001 Part C

Two subjects died in Study IP157 Part C. Subject 050-7010 was a 52 year old with a history of diabetes mellitus, hypertension and cardiovascular disease who experienced cardiac arrest 65 days after his 6th dose of study drug. The investigator considered the relationship to drug as "remotely possible". Subject 078-7012 was a 45 year old male with a history of hypertension and erectile dysfunction who experienced a myocardial infarction approximately 41 days after his 4th dose of study drug. The investigator considered the relationship to study drug as "definitely not related".

In the original NDA, a total of eight (6.2%) subjects experienced at least one SAE during the treatment period in Part C. No single SAE was reported in more than 1 subject. The eight SAE terms reported were: ischemic colitis, faecaloma, intervertebral disc protusion, wrist fracture, worsening spinal column stenosis, myocardial infarction, deep vein thrombosis (DVT), and urinary tract infection/prostatitis. Only one of these was judged by the investigator to be at least possibly related to treatment (Patient 018-7078, DVT, possibly related).

One additional patient who participated in Part C had an SAE of prostate cancer reported on Day 196 of treatment (during Part C2, the long-term safety extension of Part C). The investigator's judged this adverse event as "probably related" to treatment.

In the original NDA, study medication was permanently discontinued due to adverse events in five patients (3.8%) in Part C, for the following reasons: acne, mood swings, myocardial infarction, increased estradiol and DVT. There was no single event resulting in discontinuation that was reported in more than one subject during this study. Of the adverse events leading to discontinuation, all but myocardial infarction were judged by the investigator to be at least possibly related to study drug.

In the second Complete Response, the Sponsor updated the safety results from Study IP157-001 Parts C, including Part C2 (an additional 40 subjects). With continued dosing out to 9 injections of TU, a total of 22 subjects (14%) reported an SAE. The only SAEs, irrespective of the investigator's assessment of causality, reported by more than 1 subject were prostate cancer (in 3 subjects), spinal column stenosis (in 3 subjects), intervertebral disc disorder (in 2 subjects), and myocardial infarction (in 2 subjects). In addition, with up to 9 doses administered, a total of 16 subjects (10.5%) discontinued treatment due to AEs, irrespective of the investigator's assessment of causality. The only AEs leading to study discontinuation reported by more than 1 subject were: prostate cancer (in 3 subjects); and hematocrit increased, mood swings, anxiety, and myocardial infarction (in 2 subjects each).

Thus, the SAEs and AEs leading to discontinuation in Part C were qualitatively consistent between the original NDA and the second Complete Response, despite a longer duration of dosing.

There was one patient in Part C who experienced an immediate post-injection reaction. Patient 050-7006, a 53 year old white male experienced a mild and non-serious "coughing fit" lasting approximately 10 minutes after his 3rd injection. The investigator reported that the patient's cough was non-productive, without wheezing and without difficulty breathing. No

intervention was given and the patient recovered completely prior to leaving the office. That patient continued on-treatment without further cough events.

Deaths, Serious Adverse Events and Discontinuations due to AEs in Study IP157-001 Part A

There were two deaths reported in the Part A study. Subject 070-4006 died as a result of a homicide (by stabbing during an altercation). Subject 078-4162 was a 68 year old male with a history of COPD, hypertension, coronary artery disease status-post triple coronary artery bypass graft surgery, hyperlipidemia, erectile dysfunction, and left bundle branch block who died due to a cerebrovascular accident 71 days after his 8th dose of study medication. The investigator consider the event to be "definitely not related" to study medication.

In the original NDA, eight (6.7%) subjects in the 750 mg group and ten (8.5%) subjects in the 1000 group experienced at least one SAE during the treatment period. Only two types of SAE were observed in more than 1 subject: atrial fibrillation in 2 subjects in the 750 mg group, and knee arthroplasty in 2 subjects in the 1000 mg group. No serious adverse events (SAEs) were judged by the investigator as being at least possibly related to study drug.

The SAE terms reported for the 750mg group were: atrial fibrillation [n=2], injury (stabbing), spinal stenosis, benign parathyroid tumor, congestive heart failure, tinnitus, acute pancreatitis, and sepsis. The SAE terms for the 1000mg group were: knee arthroplasty [n=2], spinal stenosis, arthritis, coronary artery disease, enterococcal bacteremia, malignant hepatic neoplasm, renal artery stenosis, viral gastroenteritis, prostatitis, cerebrovascular accident, and tendon rupture.

In the original NDA, study medication was permanently discontinued due to adverse events in 6 (5.0 %) patients in the 750 mg group and 4 (3.4 %) patients in the 1000 mg group. AEs judged by the investigator to be at least possibly related to study drug and leading to discontinuation were:

- Subject 027-4101 (TU 750 mg arm) - increased serum PSA.
- Subject 056-4077 (TU 1000 mg arm) - increased serum estradiol.
- Subject 040-4116 (TU 1000 mg arm) - increased red blood cell count.

The complete list of AE terms for the discontinuations reported for the 750mg group were: heat exhaustion, back pain, pain in extremity, PSA increased, prostatic intraepithelial neoplasia (PIN), and injury. The AE terms for the discontinuations for the 1000mg group were: estradiol increased, red blood cell count increased, hepatic neoplasm malignant, nasal congestion, and skin ulcer.

In the second Complete Response, the Sponsor updated the safety results from Study IP157-001 Part A, including both Stages 1 and 2. With continued dosing out to 13 injections of TU, a total of 37 subjects (15%) in both the 750 mg and 1000 mg dose groups reported an SAE. In the pooled Part A study population (750 mg and 1000 mg), the only SAEs reported by more than two patients were: coronary artery disease (in 4 patients, 1.7%); and atrial fibrillation, CVA, and prostatitis (in 3 patients each, 1.3%). In the 750 mg dose group only, only one SAE was reported by more than 1 subject: atrial fibrillation (in 2 subjects, 1.7%). In addition, with

up to 13 doses administered, in the pooled Part A study population (750 mg and 1000 mg), a total of 22 subjects (9.3%) discontinued treatment due to AEs. The only AEs leading to study discontinuation reported by more than 1 subject were: increased PSA (in 5 subjects, 4.1%); prostatic intraepithelial neoplasia (in 3 subjects, 2.5%), and increased hemoglobin (in 2 subjects, 1.7%). In the 750 mg dose group only, only one SAE was reported by more than 1 subject: atrial fibrillation (in 2 subjects, 1.7%).

Thus, the SAEs and AEs leading to discontinuation in Part A were qualitatively consistent between the original NDA and the second Complete Response, despite a longer duration of dosing.

8.1.2 Other Adverse Events

Overall Adverse Events

Overall Adverse Events in Adverse Events in Study IP157-001 Part C

In the Original NDA

In Part C, the most commonly reported adverse events, regardless of the investigator's judgment on relationship to treatment, were: acne, fatigue, cough, injection site pain, nasopharyngitis, pharyngolaryngeal pain, arthralgia, insomnia, prostatitis and sinusitis. The incidence rates are provided in Table 5 below.

A total of 7 (5.4%) patients experienced at least one severe adverse event. No event was reported as severe by more than 1 patient. The complete list of severe AE terms were: DVT, aortic aneurysm, faecaloma, urinary tract infection/prostatitis, intervertebral disc protrusion, spinal stenosis, aortic aneurysm repair, and surgery.

Table 5. Incidence of All Adverse Events Regardless of Relationship to Study Medication, Reported in at Least 2.0% of Patients in Decreasing Frequency in study IP157-001 Part C

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Acne	6 (4.6)
Fatigue	6 (4.6)
Cough	4 (3.1)
Injection Site Pain	4 (3.1)
Nasopharyngitis	4 (3.1)
Pharyngolaryngeal Pain	4 (3.1)
Arthralgia	3 (2.3)
Insomnia	3 (2.3)
Prostatitis	3 (2.3)
Sinusitis	3 (2.3)

In Part C, approximately 24% of patient experienced at least 1 adverse event *judged by the investigator to be at least possibly related to treatment*. These events were generally consistent with the known adverse reactions to testosterone replacement therapy and events commonly reported in a testosterone replacement therapy population.

The incidences of adverse events reported in Part C, without regard to attributed causality, included: acne (4.6%), fatigue (3.1%), injection site pain (3.1%), irritability (1.5%), hyperhidrosis (1.5%), hemoglobin increased (1.5%), estradiol increased (1.5%), insomnia (1.5%), mood swings (1.5%), aggression (1.5%), PSA increased (1.5%) and disturbance in attention (1.5%).

In the Complete Response (with treatment out to 9 doses):

The incidences of commonly reported adverse events in Part C, reported by >5% of subjects, with treatment out to 9 doses, without regard to attributed causality, included: acne (6.1%), fatigue (7.7%), injection site pain (5.4%), insomnia (6.9%), PSA increased (7.7%), prostatitis (7.7%), nasopharyngitis (5.4%), sinusitis (6.9%), arthralgia (6.1%), and back pain (5.4%).

The incidences of overall adverse events in Part C as judged by the investigator to be at least possibly related to treatment, with treatment out to 9 doses, reported by at least 2% of subjects (n=130), included: acne (6.1%), injection site pain (5.4%), PSA increased (5.4%), fatigue (4.6%), estradiol increased (3%), irritability (2.3%), hematocrit increased (2.3%), hemoglobin increased (2.3%), insomnia (2.3%), and mood swings (2.3%).

Thus, the quality and general incidence of overall adverse events in Part C were consistent between the original NDA and the second Complete Response.

Overall Adverse Events in Adverse Events in Study IP157-001 Part A

In the Original NDA

In Part A, for the 750mg dose, the most commonly reported adverse events (≥ 2%), regardless of the investigator's judgment on relationship to treatment, were: fatigue, bronchitis, upper respiratory tract infection, nasopharyngitis, back pain, PSA increased, urinary tract infection, weight increased, hypertension, sinusitis, insomnia, nausea, and hypercholesterolemia.

In Part A, for the 1000mg dose, the most commonly reported adverse events (≥ 2%), regardless of the investigator's judgment on relationship to treatment, were: upper respiratory tract infection, diarrhea, pain in extremity, nasopharyngitis, hypertension, sinusitis, insomnia, headache, depression, weight increased, procedural pain, arthralgia, musculoskeletal pain, urinary tract infection, rash, pain, foot fracture, muscle strain, anxiety, nasal congestion, abdominal pain, constipation, vomiting, gout, benign prostatic hyperplasia, and cough.

The incidence rates for these AEs in Part A are provided in Table 6 below.

The majority of adverse events in Part A were judged by the investigator as mild or moderate in severity. Severe AEs were reported in 8.3% of 750 mg subjects and in 7.0% of 1000 mg

patients. Atrial fibrillation was reported as a severe AE in 2 subjects in the TU 750 mg group; no other single event was reported as severe in more than 1 subject per treatment group. The other severe adverse events (regardless of investigator-attributed causality) were: cardiac failure, coronary artery disease, chest discomfort, irritability, sudden hearing loss, and PSA increased.

In Part A, approximately 20% of patients in each treatment group experienced at least 1 adverse event *judged by the investigator to be at least possibly related to treatment*. These drug-related adverse events included:

> For the 750mg group: PSA increased (3.3%), insomnia (2.5%), fatigue (2.5%), injection site pain (1.7%), libido decreased (1.7%), hypercholesterolemia (1.7%), and benign prostatic hyperplasia (0.8%).
>
> For the 1000mg group: injection site pain (1.7%), benign prostatic hyperplasia (1.7%), blood cholesterol increases (1.7%), estradiol increased (1.7%), fatigue (0.9%), and insomnia (0.9%).

Table 6. Incidence of All Adverse Events Regardless of Relationship to Study Medication, Reported in at Least 2.0% of Patients in Either Treatment Group, by Preferred Term, in Decreasing Frequency in TU 1000 mg arm, from study IP157-001 Part A

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE	70 (58.3)	73 (62.4)
Upper respiratory tract infection	5 (4.2)	5 (4.3)
Diarrhoea	2 (1.7)	5 (4.3)
Pain in extremity	2 (1.7)	4 (3.4)
Nasopharyngitis	5 (4.2)	4 (3.4)
Hypertension	3 (2.5)	4 (3.4)
Sinusitis	3 (2.5)	4 (3.4)
Insomnia	3 (2.5)	4 (3.4)
Headache	2 (1.7)	4 (3.4)
Depression	2 (1.7)	4 (3.4)
Weight increased	3 (2.5)	4 (3.4)
Procedural pain	0 (0.0)	3 (2.6)
Arthralgia	2 (1.7)	3 (2.6)
Musculoskeletal pain	1 (0.8)	3 (2.6)
Urinary tract infection	3 (2.5)	3 (2.6)
Rash	1 (0.8)	3 (2.6)
Pain	0 (0.0)	3 (2.6)
Foot fracture	0 (0.0)	3 (2.6)
Muscle strain	0 (0.0)	3 (2.6)
Anxiety	0 (0.0)	3 (2.6)
Nasal congestion	0 (0.0)	3 (2.6)
Abdominal pain	0 (0.0)	3 (2.6)
Constipation	0 (0.0)	3 (2.6)
Vomiting	1 (0.8)	3 (2.6)
Gout	0 (0.0)	3 (2.6)
Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
Cough	1 (0.8)	3 (2.6)
Fatigue	7 (5.8)	2 (1.7)
Bronchitis	5 (4.2)	2 (1.7)
Back pain	4 (3.3)	2 (1.7)
Nausea	3 (2.5)	2 (1.7)
Prostatic specific antigen increased	4 (3.3)	1 (0.9)
Hypercholesterolaemia	3 (2.5)	1 (0.9)

In the Complete Response (with treatment out to 13 doses):

In Part A, for the combined 750mg and 100 mg dose groups, the most commonly reported adverse events (>5% in either dose group – with overall incidences shown in parenthesis next to the AE term), regardless of the investigator's judgment on causality, were: fatigue (6.3%), bronchitis (4.2%), upper respiratory tract infection (6.8%), nasopharyngitis (5.5%), back pain (5.5%), PSA increased (5.5%), urinary tract infection (4.6%), hypertension (7.6%), sinusitis (7.2%), insomnia (5.1%), nausea (3.8%), diarrhea (3.8%), pain in extremity (4.6%), headache (4.2%), depression (4.2%), injection site pain (4.6%), arthralgia (4.2%), musculoskeletal pain (4.2%), anxiety (3.0%), constipation (3.0%), prostatitis (5.1%), dysuria (3.4%), erectile dysfunction (3.8%), and sleep apnea syndrome (3.8%).

Thus, the quality and general incidence of overall adverse events in Part A were consistent between the original NDA and the second Complete Response.

Laboratory and vital signs data are discussed in the medical officer's reviews of the original NDA, and these data did not provide any signal of concern.

Adverse Events of Interest

In the Original NDA, "adverse events of interest" in Part C included events related to endocrine disorders, injection site reactions, adverse lipid profiles, erythropoiesis, aggression or depression, urinary symptoms, prostate health, liver abnormalities, sleep apnea syndrome, cerebrovascular events and skin events. Such adverse events were reported in 28 subjects in Part C (21.5%) as shown in *Table 7* below.

Table 7. Adverse Events of Interest in Study IP157-001 Part C

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)
			TU 750 mg LOADING (N=130)
Total Patients With At Least One TEAE of Interest			28 (21.5)
Tolerability of Injection	General disorders and administration site conditions	Injection site irritation	2 (1.5)
		Injection site pain	4 (3.1)
		Injection site rash	2 (1.5)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)
	Metabolism and Nutritional disorders	Hyperlipidemia	1 (0.8)
Erythropoiesis	Investigations	Haematocrit increased	1 (0.8)
		Haemoglobin increased	2 (1.5)
		Estradiol increased	2 (1.5)
Aggression or depression	Psychiatric disorders	Mood swings	2 (1.5)
		Aggression	2 (1.5)
Urinary Symptoms	Renal and urinary disorders	Urine flow decreased	1 (0.8)
		Nocturia	1 (0.8)
Prostate health	Investigations	Prostatic specific antigen increased	2 (1.5)
		Prostate examination abnormal	1 (0.8)
	Reproductive system and breast disorders	Prostatic intraepithelial neoplasia	1 (0.8)
		Prostatitis	3 (2.3)
		Paraesthesia of genital male	1 (0.8)
Skin	Skin and subcutaneous tissue disorders	Acne	6 (4.6)

In the second Complete Response, the adverse events of interest were anaphylaxis, POME and injection site reactions. No case of anaphylaxis and 1 case of POME was reported in Part C. Injection site pain was reported by 7 subjects (5.4%). Injection site erythema was reported by

2 subjects (1.5%) and injection site pruritis, injection site swelling, and peripheral edema were reported by 1 subject each.

In the original NDA, "adverse events of interest" in Part A were reported in 24 subjects treated with 750 mg (20%) and 30 subjects treated with 1000 mg (26%), as shown in *Table 8* below.

Table 8. Adverse Events of Interest in Study IP157-001 Part A

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
			TU 750 (N=120)	TU 1000 (N=117)
Total Patients With At Least One TEAE of Interest			**24 (20.0)**	**30 (25.6)**
Endocrine Disorder	Investigations	Oestradiol increased	0 (0.0)	2 (1.7)
		Glycosylated haemoglobin increased	0 (0.0)	1 (0.9)
	Metabolism and nutrition disorders	Diabetes mellitus	1 (0.8)	1 (0.9)
Tolerability of Injection	General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
		Injection site irritation	0 (0.0)	1 (0.9)
		Injection site pruritus	1 (0.8)	1 (0.9)
		Injection site pain	2 (1.7)	2 (1.7)
		Injection site reaction	0 (0.0)	1 (0.9)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)	2 (1.7)
		Blood triglycerides abnormal	0 (0.0)	1 (0.9)
		Blood cholesterol increased	0 (0.0)	2 (1.7)
		High density lipoprotein decreased	1 (0.8)	0 (0.0)
	Metabolism and Nutritional disorders	Hypercholesterolaemia	3 (2.5)	1 (0.9)
		Hyperlipidemia	1 (0.8)	1 (0.9)
Erythropoiesis	Investigations	Haematocrit increased	0 (0.0)	1 (0.9)
		Haemoglobin increased	0 (0.0)	1 (0.9)
		Red blood cell count increased	0 (0.0)	1 (0.9)
	Blood and lymphatic system disorders	Polycythaemia	1 (0.8)	1 (0.9)
Aggression or depression	Psychiatric disorders	Depression	2 (1.7)	4 (3.4)
Urinary Symptoms	Renal and urinary disorders	Pollakiuria	0 (0.0)	2 (1.7)
		Urinary hesitation	0 (0.0)	1 (0.9)
		Urinary retention	1 (0.8)	2 (1.7)
		Urine flow decreased	1 (0.8)	2 (1.7)
		Nocturia	0 (0.0)	1 (0.9)
		Dysuria	1 (0.8)	2 (1.7)
	Infections and infestations	Urinary tract infection	3 (2.5)	3 (2.6)
Prostate health	Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
		Prostate examination abnormal	2 (1.7)	1 (0.9)
	Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
		Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
		Prostatitis	0 (0.0)	2 (1.7)
		Prostatic disorder	1 (0.8)	0 (0.0)
Liver Abnormalities	Neoplasms benign, malignant and unspecified	Hepatic neoplasm malignant	0 (0.0)	1 (0.9)
	Investigations	Aspartate aminotransferase increased	1 (0.8)	0 (0.0)
Cerebrovascular events	Nervous system disorders	Cerebrovascular accident	0 (0.0)	1 (0.9)

In the second Complete Response, the adverse events of interest were anaphylaxis, POME and injection site reactions. No case of anaphylaxis and no case of POME was reported in Part A. Injection site pain was reported by 11 subjects overall (4.6%). Injection site swelling was reported by 3 subjects (2.6%).

8.1.3 Postmarketing Safety Findings

As demonstrated in Section 8.1.1 and 8.1.2 of this memo, in the U.S. Phase 3 study IP157-001, intramuscular testosterone undecanoate was associated with the expected adverse events and laboratory changes for a testosterone replacement agent except for 1 report of an immediate, post-injection reaction. This occurred in Patient 050-7006, a 53 year old white male, who experienced a mild and non-serious "coughing fit" lasting approximately 10 minutes after his 3rd injection.

In a different clinical study conducted outside the US (Study 306605), another case of post-injection reaction was reported. This was Patient #184, a 54 year old male who experienced urge to cough associated with respiratory distress at 1 minute after his 10th injection. Both symptoms lasted approximately 14-15 minutes.

Additional information on post-injection reactions is available from the worldwide postmarketing experience (including postmarketing clinical trials and postmarketing voluntary reporting) and this postmarketing information is important to an understanding of the potential risks of testosterone undecanoate injection.

8.1.3.1 Post-Injection Reactions in Controlled Trials

As previously noted, the Sponsor submitted safety results from 12 postmarketing clinical studies conducted outside the U.S. When these results were pooled with the results from the U.S. Study IP157-001, along with the results from the 5 European Hypogonadism studies, the total number of trials and clinical trial subjects available for analysis is 18 trials and 3,556 subjects, respectively.

As part of the review of the March 2009, first Complete Response, the Clinical review team assessed all of these studies (except for Study 14853, which was submitted as part of the second CR, was prematurely terminated, and enrolled just 3 subjects).

First, the Clinical Review team made efforts to determine whether the studies had pre-defined protocols, pre-defined procedures for capturing adverse events, and valid safety results. We then investigated the safety results themselves to determine whether any immediate post-injection reactions had been reported. The reader is referred to Dr. Handelsman's medical officer's review for brief summary reviews for each of the 11 studies submitted in the March 2009, Complete Response. Some of these studies were conducted as postmarketing European surveillance studies in hypogonadal men, whereas others were conducted for different indications, including male contraception, treatment of obesity, treatment of paraplegia, and treatment of "andropause". The two largest studies were:

1) Study AWB 0105 Androgen Deficiency – Postmarketing Surveillance, Germany, n=869, and
2) Study 39732 (NE0601 IPASS) Hypogonadism – Postmarketing Surveillance, 18 countries, n=1411.

Dr. Handelsman's review concluded that the submitted studies were of generally acceptable quality for our purpose. The studies showed the expected adverse reactions for an androgen

replacement product (e.g., increased serum PSA, worsening BPH, weight gain, edema, change in lipid profiles, acne, breast pain, sweating, depression, etc) and expected adverse reactions for an injection (e.g., injection site reactions).

As part of the review of the second Complete Response, Dr. Cynthia Kornegay, an epidemiologist in the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE) analyzed the incidence of post-injection reactions in the 18 clinical trials among the 3,556 total clinical trial subjects. She derived the data for her analysis form the Clinical Overview and Clinical Summary of Safety in the second CR. In her final review, dated March 28, 2013, Dr. Kornegay and colleagues provided the following relevant information:

1. There was one (1) POME case among the 467 men who received 750 mg TU, and eight (8) POME cases among the 3089 men who received 1000 mg TU. For both doses combined, there were 9 total adjudicated cases of POME, which translates to an incidence rate for POME of 4.5 cases per 10,000 injections, or 21.3 cases per 10,000 person-years.

2. The rates of POME in two, large, published, postmarketing studies of TU (Zitzmann et al, J Sex Med, 2013 and Gu et al, J Clin Endocrinol Metab, 2009) were similar to the rates shown in the Clinical Summary of Safety. The rates of POME shown in the Zitzman et al and the Gu et al reports were 4.8 and 5.1 POME cases per 10,000 injections, respectively

3. There were no reports of anaphylaxis among 467 men who received 750 mg TU. There were two (2) cases of anaphylaxis among 3089 men in the 1000 mg dose group. For both doses combined, there were 2 total cases of anaphylaxis, which translates to an incidence rate for anaphylaxis of 0.9 cases per 10,000 injections, or 4.7 cases per 10,000 person-years.

4. DEPI points out that published drug-related anaphylaxis rates range from 0.8 cases per 10,000 person-years to 5 cases per 10,000 person-years.

There are no additional data in the third Complete Response that contribute meaningfully to the FDA's prior analysis of the incidences POME and anaphylaxis.

8.1.3.2 Post-Injection Reactions from Voluntary Reports

The incidence of cases of post-injection reaction (POME and anaphylaxis) in clinical trials is only one piece of information that may be gleaned from the postmarketing experience. Another part of the overall safety picture is spontaneously reported adverse events from the postmarketing period.

In collaboration with the Sponsor, as well as with our colleagues Drs Stacy Chin and Tony Durmowicz from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP),

we carefully evaluated all postmarketing safety updates and all potential cases of POME and anaphylaxis submitted to Endo from the entire worldwide postmarketing experience.

From our review, we identified a total of 137 cases of severe post-injection reactions, including cases of severe POME and anaphylaxis. All 137 of these reactions were reported as severe and/or potentially life-threatening, with some cases requiring hospitalization or emergency department visit and some being treated as for anaphylaxis. The occurrence of a severe post-injection reaction is sporadic and unpredictable. These reactions have occurred after the first dose, or after 4 years of otherwise trouble-free dosing. The majority of severe post-injection reactions occur either during an injection, or immediately thereafter. The clinical manifestations of the post-injection reactions have included: cough, shortness of breath, throat-related symptoms (throat tickle, throat tightness, throat fullness, etc), flushing, various allergic-type signs and symptoms (rash, pruritis, itching), tachycardia, palpitations, blood pressure changes, and general constitutional symptoms, including headache, malaise, shivering, sweating, weakness and nausea. In rare cases, syncope, apnea, and cardiovascular collapse have been reported, however, there have been no reported deaths. The spectrum of signs and symptoms of severe POME and anaphylaxis frequently overlap, making a precise diagnosis difficult in some individual cases. Even if the mechanism for these severe post-injection reactions has not been clearly elucidated, two of the excipients, benzyl benzoate, and castor oil, may act as allergens, and castor oil itself is the likely etiology for the severe POME reactions.

In his final primary medical officer's review dated May 20, 2013, Dr. Guodong Fang, provided narratives for each of 137 severe post-injection reactions that were identified. The reader is referred to Dr. Fang's review for details on each case. Dr. Fang also provided commentary on some highlighted cases.

In their final consultative review, Drs. Chin and Durmowicz provided an assessment of anaphylaxis and POME among the potential POME and anaphylaxis cases. DPARP identified a total of 47 cases of anaphylaxis. DPARP also identified a total of 170-191 cases of POME, of which, a total of 55-76 met pre-defined criteria as being "severe". The DPARP memo provides a description of how cases were adjudicated as severe. DPARP also provides case examples for POME and anaphylaxis, as well as potential pathophysiologic mechanisms for these events.

The remainder of this section will highlight the most relevant clinical safety issues from Dr. Fang's primary medical officer review and from the DPARP consult, as it pertains to severe post-injection reactions from voluntary postmarketing adverse event reports.

1. FDA reviewed all potential postmarketing cases of POME and anaphylaxis that were included in the second Complete Response. FDA elected to focus on the severe cases from the series. With this objective in mind, FDA pre-determined the following criteria to define a "case" of severe post-injection reaction to testosterone undecanoate:
   - Occurred within 24 hours of injection and met any of the following criteria:

- Any case identified by either FDA or Sponsor as an anaphylactic reaction as a consequence of the reporter using the term “anaphylaxis” or “anaphylactic reaction”
- Any case identified by either FDA or the Sponsor as an anaphylactic reaction by meeting the formal Sampson’s criteria
- Any case identified as a serious adverse event (SAE), based upon the FDA standard definition of an SAE
- Any case requiring treatment
- Any case labeled as “Serious” or “Medically Important” by the reporter or by the Sponsor
- Any case that FDA believed to be medically significant
- Any case involving syncope or sudden lowering of the blood pressure.

2. The complete list of all 137 cases is shown in Table 7.9 of Dr. Fang’s Clinical review.

3. Most, but not all, severe post-injection reactions took place within 30 minutes of injection. A few cases occurred after 30 minutes, but all within 1 hour. Of the 137 cases, 43 occurred during the injection, 51 occurred immediately after the injection, 9 occurred within 2 to 10 minutes, 3 occurred within 60 minutes, 1 occurred within 1-8 hours, and 5 occurred within 24 hours. The exact time was not specified in 25 cases, but the event was reported on the same date as the injection.

4. Of the 137 cases, 32 (23%) were either hospitalized or were seen in the emergency department, 9 (7%) were described as life-threatening, and 19 (14%) contained a statement that blood pressure dropped or syncope occurred.

5. Of the 137 cases, 60 (44%) received some form of treatment. A total of 13 (10%) received epinephrine, 38 (28%) received corticosteroids, 30 (22%) received an antihistamine, and 18 (13%) received other therapies.

6. In conducting their assessment and adjudication of cases, DPARP used the criteria set out by the National Institute of Allergy and Infectious Disease (NIAID) and Food, Allergy and Anaphylaxis Network (FAAN) to identify cases consistent with anaphylaxis (Sampson et al, J Allergy Clin Immunol, 2006). Generally, DPARP takes the approach that anaphylaxis is identified when NIAID/FAAN criterion #1 is met; that is, acute onset of illness with involvement of the skin, mucosa or both and one of the following: respiratory compromise of reduced BP or its associated symptoms (e.g. syncope). DPARP also conducted a secondary analysis using less restrictive identification criteria (e.g., either criterion #1 or criterion #2 to identify a case of anaphylaxis) as they believed it a reasonable approach in the circumstance of TU injection where components of the products are known potential allergens.

7. DPARP reviewed case narratives for 330 potential cases of anaphylaxis. DPARP identified a total of 47 anaphylaxis cases (using just NIAID/FAAN criterion #1). If the identification criteria were less restrictive (NIAID/FAAN criteria #1 or #2), then DPARP identified a total of 68 cases. Additional anaphylaxis cases were identified in the final

Safety Update to the NDA, raising the totals to 53 and 76 cases of anaphylaxis, using strict and less restrictive identification criteria, respectively.

8. Together with DBRUP, the DPARP reviewers evaluated case narratives for 533 potential cases of POME. DPARP and DBRUP identified 170-191 POME cases (the range is due to overlap in identifying anaphylaxis using either the strict or less restrictive NIAID/FAAN criteria and thus, greater or fewer POME cases). Of these, 55-76 cases were identified as severe POME. Another 6-8 POME cases were identified in the final Safety Update to the second Complete Response.

   Additional comments and conclusions from DPARP consult are shown in Section 11 (Other Relevant Regulatory Issues) of this review.

9. Despite the inherent challenges and weaknesses in calculating postmarketing adverse event reporting rates, the Sponsor provided estimates of the reporting rates for anaphylaxis and POME for testosterone undecanoate injection. These estimates are shown in detail in Tables 7.7 and 7.8 of Dr. Fang's review. It is notable that there were two separate adjudications conducted by Sponsor, the original adjudication conducted by Endo's own internal reviewers and a later adjudication, conducted by "Internal Adjudicators" hired by Endo to re-assess these cases. The second assessment found essentially the same number of POME cases as the first assessment, but fewer anaphylaxis cases, based on a different identification criteria strategy.

   - Based on the Endo original adjudication, 79 cases of anaphylaxis were identified. With (b) (4) ampoules of TU injection sold, the reporting rate comes to (b) (4) anaphylaxis cases per 10,000 ampoules sold, or (b) (4) anaphylaxis cases per 10,000 treatment-years, assuming all ampoules sold were used in treatment.

   - Based on the "independent" adjudication, 45 cases of anaphylaxis were identified. With (b) (4) ampoules of TU injection sold, the reporting rate comes to (b) (4) anaphylaxis cases per 10,000 ampoules sold, or (b) (4) anaphylaxis cases per 10,000 treatment-years, assuming all ampoules sold were used in treatment.

   - Based on the Endo original adjudication, 228 cases of POME were identified. With (b) (4) ampoules of TU injection sold, the reporting rate comes to (b) (4) POME cases per 10,000 ampoules sold, or (b) (4) POME cases per 10,000 treatment-years, assuming all ampoules sold were used in treatment.

8.1.4 Overall Assessment of Safety Findings

My overall assessment of these safety findings is that intramuscular testosterone undecanoate has been associated with infrequent reports of severe post-injection reaction, which reflect both serious POME and anaphylaxis. There has been no reported case of death or permanent disability. However, the serious POME and anaphylaxis events have shown some severe signs and symptoms including severe cough, dyspnea, throat-related symptoms, and in rare cases, syncope, respiratory distress and instability in vital signs. Patients have been treated as if for

anaphylaxis. Some patients were hospitalized or were transported to the emergency department. Severe post-injection reactions are acute events that occur during or soon after injection. In some cases, mild events have been followed by severe events. In some cases, trouble-free dosing has been interrupted by a severe post-injection reaction after years have passed.

Aside from the severe post-injection reaction, the remainder of the safety results from clinical trials of testosterone undecanoate injection revealed the expected adverse reactions associated with the pharmacological action of testosterone (e.g., increased serum PSA, worsening BPH, weight gain, edema, change in lipid profiles, acne, breast pain, sweating, depression, etc) and expected adverse reactions for an injection (e.g., injection site reactions)

In my opinion, the Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) is appropriately constructed and well-focused on the major potential risk for this product; that is, the potential for rare events of serious POME and anaphylaxis. I agree with Dr. Fang that the REMS serves to assure safe use by bringing the main safety concern under control.

9. Advisory Committee Meeting

On April 18, 2013, a joint meeting of the Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees was held to discuss the efficacy and safety of the new drug application for testosterone undecanoate intramuscular injection. The safety discussion focused on postmarketing reports of oil microembolism in the lungs and anaphylaxis.

During the Advisory Committee Meeting on April 18, 2013, the committee voted on the following two questions:

#	Questions	Voting Results	
		Yes	No
1	Given the severe post-injection reactions that were reported with TU in clinical studies and postmarketing experience, do you believe that TU is safe for the proposed indication?	**9**	**9**
2	Whether you vote "Yes or No" to Question 1, please vote whether the Applicant's proposed instructions for use in product labeling that TU be administered using a slow (30-60 second) injection, and that patients remain in the office for 30 minutes post-injection would be sufficient to ameliorate the risk of severe post-injection reactions.	**1**	**17**

Overall, for Question #1, the voting results did not indicate a majority decision whether testosterone undecanoate (TU) was safe for the proposed indication.

Those who voted "Yes" expressed their concerns that the sponsor, Endo Pharmaceuticals, was being evaluated at a higher standard, and that the Agency set forth very challenging remediation criteria, such as change in formulation. Those who voted "Yes" also remarked that this drug has been used in Europe for many years and there have been no reported deaths. It

was also stated that there is a clear indication for treatment and a long-acting, injectable testosterone replacement would be a welcome option for treatment. In terms of the risk, including anaphylaxis and pulmonary oil microembolism (POME), the panel members who voted "Yes" remarked that these incidents have been reported as complications from the use of other medications, including testosterone injections. It was also stated that it is impossible to prevent all risks with all medications. It was also noted that indeed there is a potential improvement in compliance with this formulation.

For those who voted "No", some stated that the risks of TU injection outweighed the benefits. Those who voted "No" remarked that the product may have some potential benefit, but it also can pose potential harm. There was concern that once this is product is marketed in the U.S., the possible increase in usage could increase the number of adverse events. It was also noted that the Agency was persuasive in communicating their concerns.

The AC members did note that if the drug product was approved by the Agency, the FDA should consider including a Black Box warning as part of the labeling and a detailed patient package insert while continuing to monitor for safety and follow up as appropriate.

For Question #2, all but one member voted "No". There was a general consensus to strengthen the REMS proposal from the Sponsor (which was a Communication Plan only) to assure that the educational material is readable and usable by prescribers and patients. In addition, there should be a training program for physicians who are going to administer this medication. The FDA might consider placing limitations on the health care sites where the product is offered to assure ability to provide resuscitation should a severe post-injection reaction occur. In addition to a Black Box warning, some of the panel members recommended that the indication be narrowed. It was discussed that TU injection not be a medication of first choice and there should be efforts to define and narrow its use.

In addition, it was emphasized that early reporting of pharmacovigilance efforts was necessary to determine how this information is being communicated to patients and physicians. It was discussed that it is critical to make sure that the health care provider and patient education is assessed on a periodic basis to assure it is effective.

10. Pediatrics

The Applicant requested a full waiver of the requirement to conduct assessments in pediatric patients. The Sponsor stated that it is not likely to be used in a substantial number of pediatric patients. On April 29, 2009, the Division recommended to the Pediatric Review Committee (PeRC) that the Sponsor's request be granted. The PeRC agreed with the request but asked that the Sponsor confirm that it does not intend to apply for pediatric exclusivity in future submissions. On June 15, 2009, the Sponsor submitted a formal letter confirming that they had no intent to seek pediatric exclusivity. On July 2, 2009, George Greely of the Pediatric and Maternal Health Staff provided an eMAIL to DRUP stating:

> "*The Aveed (testosterone undecanoate) full waiver was reviewed by the PeRC PREA Subcommittee on April 29, 2009. The Division recommended a full waiver because too*

few children with the disease/condition to study. The PeRC agreed with the Division to grant a full waiver for this product."

11. Other Relevant Regulatory Issues

Office of Prescription Drug Promotion (OPDP)

A consultation regarding labeling and the REMS materials was requested and completed by OPDP.

In his final consult report for labeling, dated February 12, 2014, Trung-Hieu (Brian) Tran provided comments and recommendation on various sections of the Package Insert (PI). Comments on the Medication Guide were provided under separate cover. Each of the OPDP comments on the PI and Medication Guide were considered by 1) the Clinical review team, 2) the discipline relevant to the appropriate section, and 3) the DBRUP management. The team, including OPDP, discussed all aspects of labeling at a series of internal labeling meetings. Where the team agreed that action was indicated, (e.g., in Section 12.1, *Mechanism of Action*), the OPDP comment was acted upon and resolved through labeling discussions with Sponsor.

In his final consult report for REMS documents, dated February 19, 2014, Trung-Hieu (Brian) Tran provided comments and recommendations on the various REMS-related documents. Each of the OPDP comments on the REMS-related materials were considered by 1) the Clinical review team, 2) the Division of Risk Management (DRISK), and 3) the DBRUP management. The team, including OPDP, discussed all aspects of the REMS documents at a series of internal meetings. Where the team agreed that action was indicated, (e.g., (b) (4)), the OPDP comment was acted upon and resolved through discussions with Sponsor.

Division of Scientific Investigation (DSI)

Site inspections by the Division of Scientific Investigation were not requested. Clinical site inspections were not required as this was not a new molecular entity and the primary endpoint was a strict laboratory value (testosterone concentrations), not liable to subjective bias. Further, the Office of Clinical Pharmacology found that the assay methodology for measurement of testosterone was valid. In addition, no sites appeared unusual in terms of efficacy or adverse event reporting.

Financial Disclosure

All of the clinical investigators in the United States pivotal Phase 3 Study IP157-001 (42 out of 42 investigators at the U.S. clinical sites [only 31 sites actually enrolled subjects]) responded to request for financial disclosure and none had any relevant financial disclosure information to declare. There were no investigators with a proprietary interest in the product and none with significant equity in the Sponsor as defined in 21 CFR 54.2 (b). No investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(b).

Office of Surveillance and Epidemiology: Division of Epidemiology (DEPI)

For this review cycle, DEPI was not asked to provide consultation.

In the previous review cycle, Cynthia Kornegay and Rita Ouellet-Hellstrom of DEPI provided consultative support. In their final consult dated May 28, 2013, DEPI provided insight on the relevance, validity, and applicability of postmarketing reporting rates for POME and anaphylaxis. DEPI also conducted the principal review of the POME and anaphylaxis incidence rates from controlled trials. Details of this DEPI consult are provided in other sections of this memo, and will not be repeated here.

Office of Surveillance and Epidemiology: Division of Pharmacovigilance (DPV)

For this review cycle, DPV was not asked to provide consultation.

In the previous review cycle, Teresa Rubio and Adrienne Rothstein of DPV provided consultative support. In their final consult dated February 14, 2013, DPV provided the results of a FAERS search for POME and anaphylaxis for all approved injectable testosterone products from the time of their approval to the current date. Subsequent to the search and adjudication, a total of 33 cases were identified over a 44 year period.

Office of Surveillance and Epidemiology: Division of Risk Management (DRISK)

For this review cycle, DRISK provided extensive consultative support on the proposed Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). Suzanne Robttom, Mary Willy, Cynthia LaCivita and Claudia Manzo of DRISK provided 4 reviews of REMS-related documents (on January 31, 2014, February 5, 2014, February 11, 2014 and February 22, 2014). The REMS-related documents and items for FDA review are listed in this section, along with some of the DRISK comments.

The REMS-related documents included:

- REMS Document
- REMS Supporting Document
- Health Care Provider Enrollment Form
- Health Care Setting Enrollment Form
- Health Care Provider Education Program
- Health Care Setting Education Program
- Health Care Provider Webpage
- Patient Counseling Tool
- Aveed REMS Program Introduction Piece

DRISK concluded that the proposed REMS, in principle, was consistent with the REMS outlined in the Division's, May 29, 2013, CR action letter. However, DRISK had a significant number of recommendations for revisions and improvements to the Aveed REMS Program, including:

- The Sponsor was asked to clarify how they will ensure that Aveed is not shipped until they know that the prescriber and HCP setting are certified.
- The Sponsor was asked to create a single, patient-directed educational piece focused on the risks of serious POME and anaphylaxis (e.g., the Patient Counseling Tool).
- The Sponsor was instructed to delete the Medication Guide from the REMS. It will be a part of labeling.

- The Sponsor was instructed to remove all proposed elements of the Communication Plan and replace them with a single REMS Program Introduction Piece.
- The Sponsor was instructed to make a large number of revisions (b) (4) for clarity and brevity.
- The Sponsor was asked to submit a REMS Program website.
- The Sponsor was told to update the REMS Supporting document to be consistent with all revisions to the REMS document and other REMS-related forms.

DRISK also provided significant input on the Sponsor's proposed REMS Assessment Plan.

Finally, DRISK engaged in iterative communications with DBRUP and Sponsor until all issues on REMS-related documents and other items were resolved.

Office of Surveillance and Epidemiology: Division of Medication Error Prevention and Analysis (DMEPA)

For this review cycle, DMEPA provided consultation on the container/carton and Package Insert labeling from the medications errors perspective; as well as on the tradename.

In their final review dated February 11, 2014, Justine Harris and Lisa Khosla stated that the container and carton labeling had been revised appropriately and was acceptable.

Also, in a final review dated February 11, 2014, Justine Harris and Lisa Khosla provided recommendation for edits to Section 2 (Dosage and Administration) of the Package Insert. DMEPA's recommendations for the PI were conveyed to Sponsor and all were accepted.

Lastly, in a final review dated February 14, 2014, Justine Harris and Lisa Khosla stated that in a review dated March 14, 2013 (OSE Review #2013-2995), DMEPA found the proposed tradename, Aveed, acceptable. In that review, DMEPA stated that the proprietary name must be re-reviewed within 90 days of the anticipated approval date. DMEPA no longer re-reviews proprietary names within 90 days of approval, unless there is a change in the product characteristics. Since there has been no change to the characteristics of Aveed, the proposed tradename remains acceptable, with no objections from DMEPA.

Office of Medical Policy / Division of Medical Policy Programs (DMPP)

In their final review dated February 4, 2014, Trung-Hieu (Brian) Tran, Shawna Hutchins and Melissa Hulett provided recommendations for edits to the proposed Medication Guide. These recommendations were intended to

- improve consistency between the PI and the MedGuide,
- improve readability and reduce redundancy,
- ensure that MedGuide meets the criteria in FDA's Guidance on Consumner Medication Information
- remove promotional language.

DMPP's recommendations were conveyed to the Sponsor and all DMPP-related issues in the MedGuide were resolved through iterative labeling correspondences with Sponsor.

Study Endpoints and Labeling Development Team (SEALD)

In their final review, dated February 10, 2014, Abimbola Adebowale and Eric Brodsky provide 5 recommendations for revision to the label so that it is in compliance with labeling regulations. These 5 items were revised accordingly.

Office of Compliance

For this review cycle, Office of Compliance issued an Acceptable recommendation in EES on January 24, 2014.

Controlled Substances Staff (CSS)

DBRUP requested a consult from CSS to verify the scheduling status of Aveed (Schedule III of the Controlled Substances Act) and to assess the labeling as it applies to Section 9, Abuse and Dependence.

For this review cycle, Alicja Lerner and Michael Klein provided three consult reports, including an original consult (final dated January 24, 2014), and two Addenda (finals dated February 4, 2014 and February 18, 2014).

In their original consult, CSS provided recommendations for extensive changes to Section 9 (Drug Abuse and Dependence). CSS's second consult provided only one change (addition of one word, "*homicides*") to their original recommendation. Subsequent to receiving these two consult reports, DBRUP arranged an internal meeting with CSS and other relevant review disciplines, including DEPI and DPV, to discuss a path forward for the CSS recommendations. It was decided by the team, including CSS, that the proposed labeling changes require additional review and consideration by DBRUP and by OSE before they could be enacted for Aveed or for the drug class. Therefore, in their third and final consult report, CSS stated that "*…CSS's recommended labeling changes will not be instituted at this time. CSS will collaborate with OND and OSE on the assessment of the evidence outside the review of Aveed*

application, and final regulatory decision(s) will most likely apply to all testosterone products, including Aveed."

Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

For this review cycle, DPARP was not asked to provide consultation.

However, DPARP provided consultative support to DBRUP on each of the previous 3 review cycles in regard to the events of post-injection pulmonary oil microembolism (POME) and anaphylaxis.

Rather than describing each DPARP consultation, this section provides information only from the most recent DPARP consultation. The reader may refer to previous CDTL memos for a summary of DPARP's two prior consults.

For the third review cycle (of the second Complete Response), and as part of FDA's preparation for the April 18, 2013, Advisory Committee meeting, DPARP was again asked to adjudicate potential cases of POME and anaphylaxis in the postmarketing period.

As discussed earlier in this memo (Section 8.1.3.2), and as documented in their final consult dated March 22, 2013, DPARP reviewed case narratives for 330 potential cases of anaphylaxis. DPARP identified a total of 47 anaphylaxis cases (using just NIAID/FAAN criterion #1). If the identification criteria used were less restrictive (NAIAID/FAAN criteria #1 *or* #2), then DPARP identified a total of 68 cases. Additional anaphylaxis cases were identified in the Sponsor's final Safety Update to the second Complete Response, raising the totals to 53 and 76 cases of anaphylaxis, using strict and less restrictive identification criteria, respectively.

DPARP reviewers also assisted DBRUP in the evaluation of 533 potential cases of POME. DPARP and DBRUP identified 170-191 POME cases (the range is due to overlap as a consequence of overlap in identifying anaphylaxis using either the strict or less restrictive criteria and thus, resulting in greater or fewer POME cases). Of these, 55-76 cases were identified as severe POME. Another 6-8 POME cases were identified in the application's final Safety Update to the second Complete Response.

Based on these findings, the final conclusions and recommendations offered by DPARP (Stacy Chin, Tony Durmowicz, and Badrul Chowdhury) were consistent with their conclusions and recommendation from their prior consults:

- The safety signals of anaphylaxis and severe POME identified in previous submissions were confirmed.
- No less than 53 cases of anaphylaxis were identified in this review.
- No less than 170 cases of POME were identified, and of those at least 55 (to 76) cases were severe in intensity.

- The severity of the POME episodes are due, at least in part, to decreased cardiac output as a result of acute pulmonary hypertension (due to oil microembolism) resulting in dyspnea, dizziness and rarely, collapse.
- It is likely that POME also results in pulmonary inflammatory changes with a similar pathology to that observed in patients and in animal models of fat embolism.
- The long-term consequence of POME events, including repeated "low-grade POME" is unknown. POME that doesn't manifest as an acute event may nonetheless be harmful to lung tissue.
- As in prior consults, DPARP concluded: "*Ultimately, the decision to approve or not approve TU is a risk versus benefit decision and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.*"

12. Labeling

Labeling discussions were held during the original NDA review, as well as during the review of the second and third Complete Responses.

During this review cycle, the Sponsor and FDA worked collaboratively to generate a label that accurately described the efficacy and safety results for Aveed and that would allow for safe and effective use of Aveed. The highlights of the label include: a Boxed Warning for serious POME and anaphylaxis and a restricted Indication. The Warning describes the existence of the Aveed REMS program, the potential for serious POME and anaphylaxis, and the need to observe the patient in the healthcare setting for 30 minutes after each injection. The restricted indication is intended to narrow the target population to patients in whom the benefits of Aveed (effective testosterone replacement using the 10-week dosing interval) outweigh the potential risks of serious POME and anaphylaxis.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that the NDA be approved at this time. I am convinced that the new Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) mitigates the potential adverse consequences of the rare serious POME and anaphylaxis reactions such that the benefit of Aveed now outweighs its potential risks in the restricted target population. In order to receive the product, health care providers will need to be specially certified. Product will only come from certified distributors. Health care providers will be trained in proper administration of the product. Health care providers will attest to their awareness of the risk of serious POME and anaphylaxis, their ability to manage the rare potential severe post-injection event, and their willingness to keep the patient under observation in the health care facility for 30 minutes. Patients will be thoroughly informed of the potential risk of serious POME and anaphylaxis.

13.2 Risk Benefit Assessment

Aveed confers the expected benefit for a testosterone replacement therapy (TRT), with the need for fewer injections per year compared to other injectable TRT products. In a subgroup of patients, especially those who currently receive bimonthly IM injections, Aveed offers an option to meet their testosterone replacement needs with 6 or 7 injections per year.

The risks of Aveed include the usual androgen-related side effects plus the potential for rare serious POME and anaphylaxis reactions after the injection. In 19 clinical trials of intramuscular testosterone, at various doses and dose regimens, in approximately 3600 subjects, there were 9 reported events of POME and 2 of anaphylaxis. In approximately 8 years of postmarketing experience with intramuscular testosterone undecanoate outside the United States, mostly at a dose of 1000 mg (4 mL) per injection, we identified 137 cases of severe POME or anaphylaxis. In an additional 19 months of postmarketing experience, the information on POME and anaphylaxis remains qualitatively the same with no apparent increase in reporting rates for these events. Although some of the events have been reported as serious, with hospitalization or emergency room visit in some cases, no case has led to death or permanent disability.

With the new comprehensive Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) in place to mitigate the potential adverse consequences of the rare serious POME and anaphylaxis reactions, and an awareness by the provider and the patient of the potential serious risks, I am persuaded that the benefit of Aveed outweighs its potential risks in the restricted target population.

The reader is referred to previous sections of this memo, including the Executive Summary and Safety Summary sections for additional discussion and detail.

13.3 Recommendation for Postmarketing Risk Management Activities

The postmarketing risk management activities for Aveed are extensive. The approved REMS-related documents will include:

- REMS Document
- REMS Supporting Document
- Health Care Provider Enrollment Form
- Health Care Setting Enrollment Form
- Health Care Provider Education Program
- Health Care Setting Education Program
- Health Care Provider Webpage
- Patient Counseling Tool
- Aveed REMS Program Introduction Piece

The REMS with ETASU will assure safe use by enforcing a restricted distribution of the product only to certified prescribers who are aware of the product risks, who are trained to administer the product properly, who will inform the patient of these risks, and who will observe the patient for 30 minutes in the healthcare setting in order to manage the

consequences of a serious POME or anaphylactic reaction, in the unlikely event of such an occurrence.

In conjunction with our colleagues in DRISK, I conclude that the proposed REMS is consistent with the REMS requested by FDA in our May 29, 2013, CR action letter.

13.4 Recommendation for other Postmarketing Study Commitments

In addition to the comprehensive REMS with ETASU, we recommend that Sponsor conduct "enhanced" pharmacovigilance, such that cases of serious POME or anaphylaxis are reported to FDA within 15 days, are followed up thoroughly by Sponsor using a pre-defined and comprehensive inquiry methodology, and are reported in detail in quarterly summary safety update reports.

13.5 Recommended Comments to Applicant

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK S HIRSCH
02/28/2014

CHRISTINE P NGUYEN
02/28/2014
I concur with Dr. Hirsch's overall recommendation of approval.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CIALIS safely and effectively. See full prescribing information for CIALIS.

CIALIS (tadalafil) tablets, for oral use
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.4) 05/2017

----------INDICATIONS AND USAGE----------

CIALIS® is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of:
- erectile dysfunction (ED) (1.1)
- the signs and symptoms of benign prostatic hyperplasia (BPH) (1.2)
- ED and the signs and symptoms of BPH (ED/BPH) (1.3)

If CIALIS is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks (1.4).

----------DOSAGE AND ADMINISTRATION----------
- *CIALIS for use as needed:*
- ED: Starting dose: 10 mg as needed prior to sexual activity. Increase to 20 mg or decrease to 5 mg based upon efficacy/tolerability. Improves erectile function compared to placebo up to 36 hours post dose. Not to be taken more than once per day (2.1).
- *CIALIS for once daily use:*
- ED: 2.5 mg taken once daily, without regard to timing of sexual activity. May increase to 5 mg based upon efficacy and tolerability (2.2).
- BPH: 5 mg, taken at approximately the same time every day (2.3)
- ED and BPH: 5 mg, taken at approximately the same time every day (2.3, 2.4)
- CIALIS may be taken without regard to food (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 2.5 mg, 5 mg, 10 mg, 20 mg (3).

----------CONTRAINDICATIONS----------
- Administration of CIALIS to patients using any form of organic nitrate is contraindicated. CIALIS was shown to potentiate the hypotensive effect of nitrates (4.1).
- History of known serious hypersensitivity reaction to CIALIS or ADCIRCA® (4.2).
- Administration with guanylate cyclase (GC) stimulators, such as riociguat (4.3).

----------WARNINGS AND PRECAUTIONS----------
- Patients should not use CIALIS if sex is inadvisable due to cardiovascular status (5.1).
- Use of CIALIS with alpha-blockers, antihypertensives or substantial amounts of alcohol (≥5 units) may lead to hypotension (5.6, 5.9).
- CIALIS is not recommended in combination with alpha-blockers for the treatment of BPH because efficacy of the combination has not been adequately studied and because of the risk of blood pressure lowering. Caution is advised when CIALIS is used as a treatment for ED in men taking alpha-blockers. (2.7, 5.6, 7.1, 12.2)
- Patients should seek emergency treatment if an erection lasts >4 hours. Use CIALIS with caution in patients predisposed to priapism (5.3).
- Patients should stop CIALIS and seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION). CIALIS should be used with caution, and only when the anticipated benefits outweigh the risks, in patients with a history of NAION. Patients with a "crowded" optic disc may also be at an increased risk of NAION (5.4, 6.2).
- Patients should stop CIALIS and seek prompt medical attention in the event of sudden decrease or loss of hearing (5.5).
- Prior to initiating treatment with CIALIS for BPH, consideration should be given to other urological conditions that may cause similar symptoms (5.14).

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥2%) include headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- CIALIS can potentiate the hypotensive effects of nitrates, alpha-blockers, antihypertensives or alcohol (7.1).
- CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) increase CIALIS exposure (2.7, 5.10, 7.2) requiring dose adjustment:
  - CIALIS for use as needed: no more than 10 mg every 72 hours
  - CIALIS for once daily use: dose not to exceed 2.5 mg
- CYP3A4 inducers (e.g. rifampin) decrease CIALIS exposure (7.2).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment (2.6, 5.8, 8.6):
- Mild or Moderate: Dosage adjustment may be needed.
- Severe: Use is not recommended.

Renal Impairment (2.6, 5.7, 8.7):
- Patients with creatinine clearance 30 to 50 mL/min: Dosage adjustment may be needed.
- Patients with creatinine clearance less than 30 mL/min or on hemodialysis: For use as needed: Dose should not exceed 5 mg every 72 hours. Once daily use is not recommended.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Erectile Dysfunction

CIALIS® is indicated for the treatment of erectile dysfunction (ED).

1.2 Benign Prostatic Hyperplasia

CIALIS is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

1.3 Erectile Dysfunction and Benign Prostatic Hyperplasia

CIALIS is indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).

1.4 Limitation of Use

If CIALIS is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of CIALIS decreases from 4 weeks until 26 weeks, and the incremental benefit of CIALIS beyond 26 weeks is unknown *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

Do not split CIALIS tablets; entire dose should be taken.

2.1 CIALIS for Use as Needed for Erectile Dysfunction

- The recommended starting dose of CIALIS for use as needed in most patients is 10 mg, taken prior to anticipated sexual activity.
- The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.
- CIALIS for use as needed was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of CIALIS, this should be taken into consideration.

2.2 CIALIS for Once Daily Use for Erectile Dysfunction

- The recommended starting dose of CIALIS for once daily use is 2.5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.
- The CIALIS dose for once daily use may be increased to 5 mg, based on individual efficacy and tolerability.

2.3 CIALIS for Once Daily Use for Benign Prostatic Hyperplasia

- The recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day.
- When therapy for BPH is initiated with CIALIS and finasteride, the recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day for up to 26 weeks.

2.4 CIALIS for Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia

The recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.

2.5 Use with Food

CIALIS may be taken without regard to food.

2.6 Use in Specific Populations

Renal Impairment

CIALIS for Use as Needed

- Creatinine clearance 30 to 50 mL/min: A starting dose of 5 mg not more than once per day is recommended, and the maximum dose is 10 mg not more than once in every 48 hours.
- Creatinine clearance less than 30 mL/min or on hemodialysis: The maximum dose is 5 mg not more than once in every 72 hours *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

CIALIS for Once Daily Use

Erectile Dysfunction

- Creatinine clearance less than 30 mL/min or on hemodialysis: CIALIS for once daily use is not recommended *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

Benign Prostatic Hyperplasia and Erectile Dysfunction/Benign Prostatic Hyperplasia

- Creatinine clearance 30 to 50 mL/min: A starting dose of 2.5 mg is recommended. An increase to 5 mg may be considered based on individual response.
- Creatinine clearance less than 30 mL/min or on hemodialysis: CIALIS for once daily use is not recommended *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

Hepatic Impairment

CIALIS for Use as Needed

- Mild or moderate (Child Pugh Class A or B): The dose should not exceed 10 mg once per day. The use of CIALIS once per day has not been extensively evaluated in patients with hepatic impairment and therefore, caution is advised.
- Severe (Child Pugh Class C): The use of CIALIS is not recommended *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.6)]*.

CIALIS for Once Daily Use

- Mild or moderate (Child Pugh Class A or B): CIALIS for once daily use has not been extensively evaluated in patients with hepatic impairment. Therefore, caution is advised if CIALIS for once daily use is prescribed to these patients.
- Severe (Child Pugh Class C): The use of CIALIS is not recommended *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.6)]*.

2.7 Concomitant Medications

Nitrates

Concomitant use of nitrates in any form is contraindicated *[see Contraindications (4.1)]*.

Alpha-Blockers

ED — When CIALIS is coadministered with an alpha-blocker in patients being treated for ED, patients should be stable on alpha-blocker therapy prior to initiating treatment, and CIALIS should be initiated at the lowest recommended dose *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

BPH — CIALIS is not recommended for use in combination with alpha-blockers for the treatment of BPH *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

CYP3A4 Inhibitors

CIALIS for Use as Needed — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of CIALIS is 10 mg, not to exceed once every 72 hours *[see Warnings and Precautions (5.10) and Drug Interactions (7.2)]*.

CIALIS for Once Daily Use — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose is 2.5 mg *[see Warnings and Precautions (5.10) and Drug Interactions (7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Four strengths of almond-shaped tablets are available in different sizes and different shades of yellow:
2.5 mg tablets debossed with “C 2 1/2”
5 mg tablets debossed with “C 5”
10 mg tablets debossed with “C 10”
20 mg tablets debossed with “C 20”

4 CONTRAINDICATIONS

4.1 Nitrates

Administration of CIALIS to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, CIALIS was shown to potentiate the hypotensive effect of nitrates *[see Clinical Pharmacology (12.2)]*.

4.2 Hypersensitivity Reactions

CIALIS is contraindicated in patients with a known serious hypersensitivity to tadalafil (CIALIS or ADCIRCA®). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis *[see Adverse Reactions (6.2)]*.

4.3 Concomitant Guanylate Cyclase (GC) Stimulators

Do not use CIALIS in patients who are using a GC stimulator, such as riociguat. PDE5 inhibitors, including CIALIS, may potentiate the hypotensive effects of GC stimulators.

5 WARNINGS AND PRECAUTIONS

Evaluation of erectile dysfunction and BPH should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options.

Before prescribing CIALIS, it is important to note the following:

5.1 Cardiovascular

Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatments for erectile dysfunction, including CIALIS, should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and seek immediate medical attention.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of CIALIS. In such a patient, who has taken CIALIS, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking CIALIS should seek immediate medical attention. *[see Contraindications (4.1) and Patient Counseling Information (17.1)]*.

Patients with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators, including PDE5 inhibitors.

The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for CIALIS, and therefore until further information is available, CIALIS is not recommended for the following groups of patients:

- myocardial infarction within the last 90 days
- unstable angina or angina occurring during sexual intercourse
- New York Heart Association Class 2 or greater heart failure in the last 6 months
- uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension
- stroke within the last 6 months.

As with other PDE5 inhibitors, tadalafil has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, tadalafil 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mm Hg in healthy subjects *[see Clinical Pharmacology (12.2)]*. While this effect should not be of consequence in most patients, prior to prescribing CIALIS, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

5.2 Potential for Drug Interactions When Taking CIALIS for Once Daily Use

Physicians should be aware that CIALIS for once daily use provides continuous plasma tadalafil levels and should consider this when evaluating the potential for interactions with medications (e.g., nitrates, alpha-blockers, anti-hypertensives and potent inhibitors of CYP3A4) and with substantial consumption of alcohol *[see Drug Interactions (7.1, 7.2, 7.3)]*.

5.3 Prolonged Erection

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

CIALIS should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

5.4 Effects on the Eye

Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including CIALIS, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision, including permanent loss of vision, that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥50.

An observational case-crossover study evaluated the risk of NAION when PDE5 inhibitor use, as a class, occurred immediately before NAION onset (within 5 half-lives), compared to PDE5 inhibitor use in a prior time period. The results suggest an approximate 2-fold increase in the risk of NAION, with a risk estimate of 2.15 (95% CI 1.06, 4.34). A similar study reported a consistent result, with a risk estimate of 2.27 (95% CI 0.99, 5.20). Other risk factors for NAION, such as the presence of “crowded” optic disc, may have contributed to the occurrence of NAION in these studies.

Neither the rare postmarketing reports, nor the association of PDE5 inhibitor use and NAION in the observational studies, substantiate a causal relationship between PDE5 inhibitor use and NAION *[see Adverse Reactions (6.2)]*.

Physicians should consider whether their patients with underlying NAION risk factors could be adversely affected by use of PDE5 inhibitors. Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, PDE5 inhibitors, including CIALIS, should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with “crowded” optic disc are also considered at greater risk for NAION compared to the general population; however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including CIALIS, for this uncommon condition.

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

5.5 Sudden Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including CIALIS, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including CIALIS. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6.1, 6.2)]*.

5.6 Alpha-blockers and Antihypertensives

Physicians should discuss with patients the potential for CIALIS to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including CIALIS, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*, which may lead to symptomatic hypotension (e.g., fainting). Consideration should be given to the following:

ED

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended dose.
- In those patients already taking an optimized dose of PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.
- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other antihypertensive drugs.

[see Dosage and Administration (2.7) and Drug Interactions (7.1)].

BPH

- The efficacy of the coadministration of an alpha-blocker and CIALIS for the treatment of BPH has not been adequately studied, and due to the potential vasodilatory effects of combined use resulting in blood pressure lowering, the combination of CIALIS and alpha-blockers is not recommended for the treatment of BPH. *[see Dosage and Administration (2.7), Drug Interactions (7.1), and Clinical Pharmacology (12.2.)]*.
- Patients on alpha-blocker therapy for BPH should discontinue their alpha-blocker at least one day prior to starting CIALIS for once daily use for the treatment of BPH.

5.7 Renal Impairment

CIALIS for Use as Needed

CIALIS should be limited to 5 mg not more than once in every 72 hours in patients with creatinine clearance less than 30 mL/min or end-stage renal disease on hemodialysis. The starting dose of CIALIS in patients with creatinine

clearance 30 – 50 mL/min should be 5 mg not more than once per day, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. *[see Use in Specific Populations (8.7)]*.

CIALIS for Once Daily Use

ED

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, CIALIS for once daily use is not recommended in patients with creatinine clearance less than 30 mL/min *[see Use in Specific Populations (8.7)]*.

BPH and ED/BPH

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, CIALIS for once daily use is not recommended in patients with creatinine clearance less than 30 mL/min. In patients with creatinine clearance 30 – 50 mL/min, start dosing at 2.5 mg once daily, and increase the dose to 5 mg once daily based upon individual response *[see Dosage and Administration (2.6), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

5.8 Hepatic Impairment

CIALIS for Use as Needed

In patients with mild or moderate hepatic impairment, the dose of CIALIS should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of CIALIS in this group is not recommended *[see Use in Specific Populations (8.6)]*.

CIALIS for Once Daily Use

CIALIS for once daily use has not been extensively evaluated in patients with mild or moderate hepatic impairment. Therefore, caution is advised if CIALIS for once daily use is prescribed to these patients. Because of insufficient information in patients with severe hepatic impairment, use of CIALIS in this group is not recommended *[see Use in Specific Populations (8.6)]*.

5.9 Alcohol

Patients should be made aware that both alcohol and CIALIS, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *[see Clinical Pharmacology (12.2)]*.

5.10 Concomitant Use of Potent Inhibitors of Cytochrome P450 3A4 (CYP3A4)

CIALIS is metabolized predominantly by CYP3A4 in the liver. The dose of CIALIS for use as needed should be limited to 10 mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, and itraconazole *[see Drug Interactions (7.2)]*. In patients taking potent inhibitors of CYP3A4 and CIALIS for once daily use, the maximum recommended dose is 2.5 mg *[see Dosage and Administration (2.7)]*.

5.11 Combination With Other PDE5 Inhibitors or Erectile Dysfunction Therapies

The safety and efficacy of combinations of CIALIS and other PDE5 inhibitors or treatments for erectile dysfunction have not been studied. Inform patients not to take CIALIS with other PDE5 inhibitors, including ADCIRCA.

5.12 Effects on Bleeding

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. CIALIS has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although CIALIS has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

5.13 Counseling Patients About Sexually Transmitted Diseases

The use of CIALIS offers no protection against sexually transmitted diseases. Counseling patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

5.14 Consideration of Other Urological Conditions Prior to Initiating Treatment for BPH

Prior to initiating treatment with CIALIS for BPH, consideration should be given to other urological conditions that may cause similar symptoms. In addition, prostate cancer and BPH may coexist.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Tadalafil was administered to over 9000 men during clinical trials worldwide. In trials of CIALIS for once daily use, a total of 1434, 905, and 115 were treated for at least 6 months, 1 year, and 2 years, respectively. For CIALIS for use as needed, over 1300 and 1000 subjects were treated for at least 6 months and 1 year, respectively.

CIALIS for Use as Needed for ED

In eight primary placebo-controlled clinical studies of 12 weeks duration, mean age was 59 years (range 22 to 88) and the discontinuation rate due to adverse events in patients treated with tadalafil 10 or 20 mg was 3.1%, compared to 1.4% in placebo treated patients.

When taken as recommended in the placebo-controlled clinical trials, the following adverse reactions were reported (*see* Table 1) for CIALIS for use as needed:

Table 1: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS (10 or 20 mg) and More Frequent on Drug than Placebo in the Eight Primary Placebo-Controlled Clinical Studies (Including a Study in Patients with Diabetes) for CIALIS for Use as Needed for ED

Adverse Reaction	Placebo (N=476)	Tadalafil 5 mg (N=151)	Tadalafil 10 mg (N=394)	Tadalafil 20 mg (N=635)
Headache	5%	11%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal congestion	1%	2%	3%	3%
Flushing[a]	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

[a] The term flushing includes: facial flushing and flushing

CIALIS for Once Daily Use for ED

In three placebo-controlled clinical trials of 12 or 24 weeks duration, mean age was 58 years (range 21 to 82) and the discontinuation rate due to adverse events in patients treated with tadalafil was 4.1%, compared to 2.8% in placebo-treated patients.

The following adverse reactions were reported (*see* Table 2) in clinical trials of 12 weeks duration:

Table 2: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS for Once Daily Use (2.5 or 5 mg) and More Frequent on Drug than Placebo in the Three Primary Placebo-Controlled Phase 3 Studies of 12 weeks Treatment Duration (Including a Study in Patients with Diabetes) for CIALIS for Once Daily Use for ED

Adverse Reaction	Placebo (N=248)	Tadalafil 2.5 mg (N=196)	Tadalafil 5 mg (N=304)
Headache	5%	3%	6%
Dyspepsia	2%	4%	5%
Nasopharyngitis	4%	4%	3%
Back pain	1%	3%	3%
Upper respiratory tract infection	1%	3%	3%
Flushing	1%	1%	3%
Myalgia	1%	2%	2%
Cough	0%	4%	2%
Diarrhea	0%	1%	2%
Nasal congestion	0%	2%	2%
Pain in extremity	0%	1%	2%
Urinary tract infection	0%	2%	0%
Gastroesophageal reflux disease	0%	2%	1%
Abdominal pain	0%	2%	1%

The following adverse reactions were reported (*see* Table 3) over 24 weeks treatment duration in one placebo-controlled clinical study:

Table 3: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS for Once Daily Use (2.5 or 5 mg) and More Frequent on Drug than Placebo in One Placebo-Controlled Clinical Study of 24 Weeks Treatment Duration for CIALIS for Once Daily Use for ED

Adverse Reaction	Placebo (N=94)	Tadalafil 2.5 mg (N=96)	Tadalafil 5 mg (N=97)
Nasopharyngitis	5%	6%	6%
Gastroenteritis	2%	3%	5%
Back pain	3%	5%	2%
Upper respiratory tract infection	0%	3%	4%
Dyspepsia	1%	4%	1%
Gastroesophageal reflux disease	0%	3%	2%
Myalgia	2%	4%	1%
Hypertension	0%	1%	3%
Nasal congestion	0%	0%	4%

CIALIS for Once Daily Use for BPH and for ED and BPH

In three placebo-controlled clinical trials of 12 weeks duration, two in patients with BPH and one in patients with ED and BPH, the mean age was 63 years (range 44 to 93) and the discontinuation rate due to adverse events in patients treated with tadalafil was 3.6% compared to 1.6% in placebo-treated patients. Adverse reactions leading to discontinuation reported by at least 2 patients treated with tadalafil included headache, upper abdominal pain, and myalgia. The following adverse reactions were reported (*see* Table 4).

Table 4: Treatment-Emergent Adverse Reactions Reported by ≥1% of Patients Treated with CIALIS for Once Daily Use (5 mg) and More Frequent on Drug than Placebo in Three Placebo-Controlled Clinical Studies of 12 Weeks Treatment Duration, including Two Studies for CIALIS for Once Daily Use for BPH and One Study for ED and BPH

Adverse Reaction	Placebo (N=576)	Tadalafil 5 mg (N=581)
Headache	2.3%	4.1%
Dyspepsia	0.2%	2.4%
Back pain	1.4%	2.4%
Nasopharyngitis	1.6%	2.1%
Diarrhea	1.0%	1.4%
Pain in extremity	0.0%	1.4%
Myalgia	0.3%	1.2%
Dizziness	0.5%	1.0%

Additional, less frequent adverse reactions (<1%) reported in the controlled clinical trials of CIALIS for BPH or ED and BPH included: gastroesophageal reflux disease, upper abdominal pain, nausea, vomiting, arthralgia, and muscle spasm.

Back pain or myalgia was reported at incidence rates described in Tables 1 through 4. In tadalafil clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbency. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported with a low frequency (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required treatment, a mild narcotic (e.g., codeine) was used. Overall, approximately 0.5% of all subjects treated with CIALIS for on demand use discontinued treatment as a consequence of back pain/myalgia. In the 1-year open label extension study, back pain and myalgia were reported in 5.5% and 1.3% of patients, respectively. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology. Incidence rates for CIALIS for once daily use for ED, BPH and BPH/ED are described in Tables 2, 3 and 4. In studies of CIALIS for once daily use, adverse reactions of back pain and myalgia were generally mild or moderate with a discontinuation rate of <1% across all indications.

Across placebo-controlled studies with CIALIS for use as needed for ED, diarrhea was reported more frequently in patients 65 years of age and older who were treated with CIALIS (2.5% of patients) *[see Use in Specific Populations (8.5)]*.

Across all studies with any CIALIS dose, reports of changes in color vision were rare (<0.1% of patients).

The following section identifies additional, less frequent events (<2%) reported in controlled clinical trials of CIALIS for once daily use or use as needed. A causal relationship of these events to CIALIS is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and reports too imprecise to be meaningful:

Body as a Whole — asthenia, face edema, fatigue, pain, peripheral edema

Cardiovascular — angina pectoris, chest pain, hypotension, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia

Digestive — abnormal liver function tests, dry mouth, dysphagia, esophagitis, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting, gastroesophageal reflux disease, hemorrhoidal hemorrhage, rectal hemorrhage

Musculoskeletal — arthralgia, neck pain

Nervous — dizziness, hypesthesia, insomnia, paresthesia, somnolence, vertigo

Renal and Urinary — renal impairment

Respiratory — dyspnea, epistaxis, pharyngitis

Skin and Appendages — pruritus, rash, sweating

Ophthalmologic — blurred vision, changes in color vision, conjunctivitis (including conjunctival hyperemia), eye pain, lacrimation increase, swelling of eyelids

Otologic — sudden decrease or loss of hearing, tinnitus

Urogenital — erection increased, spontaneous penile erection

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of CIALIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors.

Cardiovascular and Cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of CIALIS without sexual activity. Others were reported to have occurred hours to days after the use of CIALIS and sexual activity. It is not possible to determine whether these events are related directly to CIALIS, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors *[see Warnings and Precautions (5.1)]*.

Body as a Whole — hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis

Nervous — migraine, seizure and seizure recurrence, transient global amnesia

Ophthalmologic — visual field defect, retinal vein occlusion, retinal artery occlusion

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including CIALIS. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking *[see Warnings and Precautions (5.4)]*.

Otologic — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including CIALIS. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of CIALIS, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors *[see Warnings and Precautions (5.5)]*.

Urogenital — priapism *[see Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

7.1 Potential for Pharmacodynamic Interactions with CIALIS

Nitrates — Administration of CIALIS to patients who are using any form of organic nitrate, is contraindicated. In clinical pharmacology studies, CIALIS was shown to potentiate the hypotensive effect of nitrates. In a patient who has taken CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Dosage and Administration (2.7), Contraindications (4.1), and Clinical Pharmacology (12.2)]*.

Alpha-Blockers — Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including CIALIS, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, tamsulosin or alfuzosin. *[see Dosage and Administration (2.7), Warnings and Precautions (5.6), and Clinical Pharmacology (12.2)]*.

Antihypertensives — PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and

metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo. *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.2)]*.

Alcohol — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations. *[see Warnings and Precautions (5.9) and Clinical Pharmacology (12.2)]*.

7.2 Potential for Other Drugs to Affect CIALIS

[See Dosage and Administration (2.7) and Warnings and Precautions (5.10)].

Antacids — Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

H_2 Antagonists (e.g. Nizatidine) — An increase in gastric pH resulting from administration of nizatidine had no significant effect on pharmacokinetics.

Cytochrome P450 Inhibitors — CIALIS is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure.

CYP3A4 (e.g., Ketoconazole) — Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20 mg single-dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10-mg single-dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for tadalafil 10 mg alone *[see Dosage and Administration (2.7)]*.

Although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure.

HIV Protease inhibitor — Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in C_{max}, relative to the values for tadalafil 20 mg alone. Ritonavir (200 mg twice daily), increased tadalafil 20-mg single-dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase tadalafil exposure *[see Dosage and Administration (2.7)]*.

Cytochrome P450 Inducers — Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure.

CYP3A4 (e.g., Rifampin) — Rifampin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10-mg single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted. The reduced exposure of tadalafil with the coadministration of rifampin or other CYP3A4 inducers can be anticipated to decrease the efficacy of CIALIS for once daily use; the magnitude of decreased efficacy is unknown.

7.3 Potential for CIALIS to Affect Other Drugs

Aspirin — Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Cytochrome P450 Substrates — CIALIS is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

CYP1A2 (e.g. Theophylline) — Tadalafil had no significant effect on the pharmacokinetics of theophylline. When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP2C9 (e.g. Warfarin) — Tadalafil had no significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin.

CYP3A4 (e.g. Midazolam or Lovastatin) — Tadalafil had no significant effect on exposure (AUC) to midazolam or lovastatin.

P-glycoprotein *(e.g. Digoxin)* — Coadministration of tadalafil (40 mg once per day) for 10 days did not have a significant effect on the steady-state pharmacokinetics of digoxin (0.25 mg/day) in healthy subjects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

CIALIS (tadalafil) is not indicated for use in females.

There are no data with the use of CIALIS in pregnant women to inform any drug-associated risks for adverse developmental outcomes. In animal reproduction studies, no adverse developmental effects were observed with oral administration of tadalafil to pregnant rats or mice during organogenesis at exposures up to 11 times the maximum recommended human dose (MRHD) of 20 mg/day (*see* Data).

Data

Animal Data

Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given orally to pregnant rats or mice at exposures up to 11 times the maximum recommended human dose (MRHD) of 20 mg/day during organogenesis. In a prenatal/postnatal developmental study in rats, postnatal pup survival decreased following maternal exposure to tadalafil doses greater than 10 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 16 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

In another rat prenatal and postnatal development study at doses of 60, 200, and 1000 mg/kg, a reduction in postnatal survival of pups was observed. The no observed effect level (NOEL) for maternal toxicity was 200 mg/kg/day and for developmental toxicity was 30 mg/kg/day. This gives approximately 16 and 10 fold exposure multiples, respectively, of the human AUC for the MRHD of 20 mg.

Tadalafil and/or its metabolites cross the placenta, resulting in fetal exposure in rats.

8.2 Lactation

Risk Summary

CIALIS is not indicated for use in females.

There is no information on the presence of tadalafil and/or metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Tadalafil and/or its metabolites are present in the milk of lactating rats at concentrations approximately 2.4-fold greater than found in the plasma.

8.3 Females and Males of Reproductive Potential

Infertility

Based on the data from 3 studies in adult males, tadalafil decreased sperm concentrations in the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. There was no adverse effect of tadalafil 10 mg or 20 mg on mean concentrations of testosterone, luteinizing hormone or follicle stimulating hormone. The clinical significance of the decreased sperm concentrations in the two studies is unknown. There have been no studies evaluating the effect of tadalafil on fertility in men *[see Clinical Pharmacology (12.2)]*.

Based on studies in animals, a decrease in spermatogenesis was observed in dogs, but not in rats *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

CIALIS is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years have not been established.

A randomized, double-blind, placebo-controlled trial in pediatric patients (7 to 14 years of age) with Duchenne muscular dystrophy, who received CIALIS 0.3 mg/kg, CIALIS 0.6 mg/kg, or placebo daily for 48 weeks failed to demonstrate any benefit of treatment with CIALIS on a range of assessments of muscle strength and performance.

Juvenile Animal Study

No adverse effects were observed in a study in which tadalafil was administered orally at doses of 60, 200, and 1000 mg/kg/day to juvenile rats on postnatal days 14 to 90. The highest plasma tadalafil exposures (AUC) achieved were approximately 10-fold that observed at the MRHD.

8.5 Geriatric Use

Of the total number of subjects in ED clinical studies of tadalafil, approximately 19 percent were 65 and over, while approximately 2 percent were 75 and over. Of the total number of subjects in BPH clinical studies of tadalafil (including the ED/BPH study), approximately 40 percent were over 65, while approximately 10 percent were 75 and over. In these clinical trials, no overall differences in efficacy or safety were observed between older (>65 and ≥75 years of age) and younger subjects (≤65 years of age). However, in placebo-controlled studies with CIALIS for use as needed for ED, diarrhea was reported more frequently in patients 65 years of age and older who were treated with CIALIS (2.5% of patients) *[see Adverse Reactions (6.1)]*. No dose adjustment is warranted based on age alone. However, a greater sensitivity to medications in some older individuals should be considered. *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C). *[see Dosage and Administration (2.6) and Warnings and Precautions (5.8)]*.

8.7 Renal Impairment

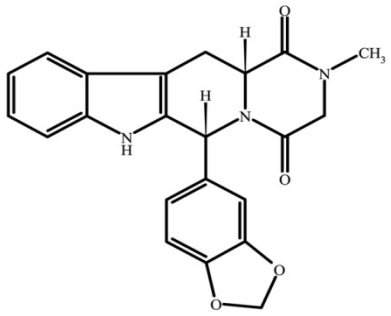
In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with creatinine clearance 30 to 80 mL/min. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.8-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with creatinine clearance 30 to 50 mL/min. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain. *[see Dosage and Administration (2.6) and Warnings and Precautions (5.7)]*.

10 OVERDOSAGE

Single doses up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Hemodialysis contributes negligibly to tadalafil elimination.

11 DESCRIPTION

CIALIS (tadalafil) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:



The chemical designation is pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

CIALIS is available as almond-shaped tablets for oral administration. Each tablet contains 2.5, 5, 10, or 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The mechanism for reducing BPH symptoms has not been established.

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in the smooth muscle of the corpus cavernosum, prostate, and bladder as well as in vascular and visceral smooth muscle, skeletal muscle, urethra, platelets, kidney, lung, cerebellum, heart, liver, testis, seminal vesicle, and pancreas.

In vitro studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10. Tadalafil is 14-fold more potent for PDE5 than for PDE11A1 and 40-fold more potent for PDE5 than for PDE11A4, two of the four known

forms of PDE11. PDE11 is an enzyme found in human prostate, testes, skeletal muscle and in other tissues (e.g., adrenal cortex). *In vitro*, tadalafil inhibits human recombinant PDE11A1 and, to a lesser degree, PDE11A4 activities at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

12.2 Pharmacodynamics

Effects on Blood Pressure

Tadalafil 20 mg administered to healthy male subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively). In addition, there was no significant effect on heart rate.

Effects on Blood Pressure When Administered with Nitrates

In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of CIALIS in patients taking any form of nitrates is contraindicated *[see Contraindications (4.1)]*.

A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre-specified timepoints, following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). The objective of the study was to determine when, after tadalafil dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood-pressure lowering at this timepoint. After 48 hours, the interaction was not detectable (*see* Figure 1).

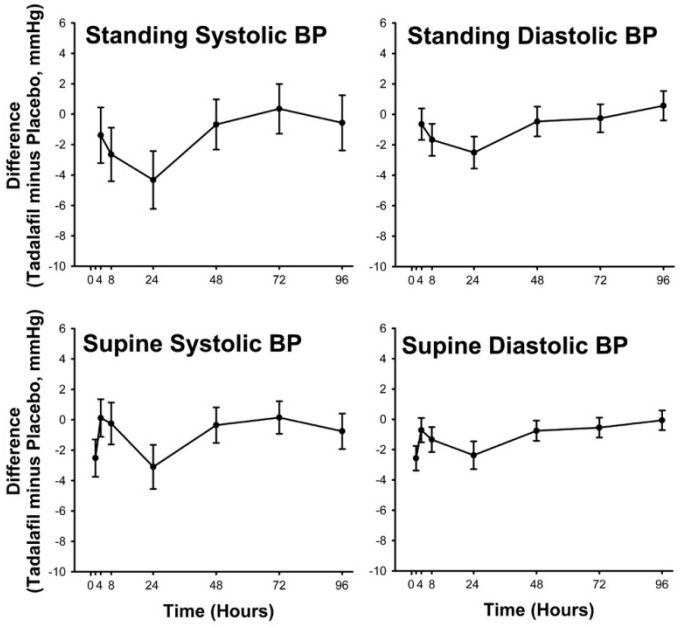


Figure 1: Mean Maximal Change in Blood Pressure (Tadalafil Minus Placebo, Point Estimate with 90% CI) in Response to Sublingual Nitroglycerin at 2 (Supine Only), 4, 8, 24, 48, 72, and 96 Hours after the Last Dose of Tadalafil 20 mg or Placebo

Therefore, CIALIS administration with nitrates is contraindicated. In a patient who has taken CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Contraindications (4.1)]*.

Effect on Blood Pressure When Administered With Alpha-Blockers

Six randomized, double-blinded, crossover clinical pharmacology studies were conducted to investigate the potential interaction of tadalafil with alpha-blocker agents in healthy male subjects *[see Dosage and Administration (2.7) and Warnings and Precautions (5.6)]*. In four studies, a single oral dose of tadalafil was administered to healthy male

subjects taking daily (at least 7 days duration) an oral alpha-blocker. In two studies, a daily oral alpha-blocker (at least 7 days duration) was administered to healthy male subjects taking repeated daily doses of tadalafil.

Doxazosin — Three clinical pharmacology studies were conducted with tadalafil and doxazosin, an alpha[1]-adrenergic blocker.

In the first doxazosin study, a single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking oral doxazosin 8 mg daily (N=18 subjects). Doxazosin was administered at the same time as tadalafil or placebo after a minimum of seven days of doxazosin dosing (*see* Table 5 and Figure 2).

Table 5: Doxazosin (8 mg/day) Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 20 mg
Supine	3.6 (-1.5, 8.8)
Standing	9.8 (4.1, 15.5)

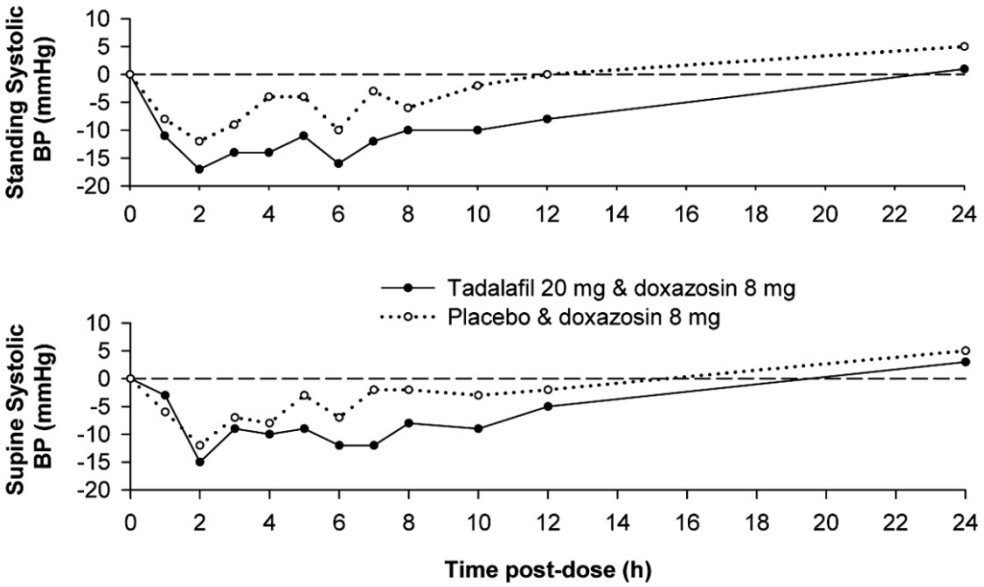


Figure 2: Doxazosin Study 1: Mean Change from Baseline in Systolic Blood Pressure

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo administration. Outliers were defined as subjects with a standing systolic blood pressure of <85 mm Hg or a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points. There were nine and three outliers following administration of tadalafil 20 mg and placebo, respectively. Five and two subjects were outliers due to a decrease from baseline in standing systolic BP of >30 mm Hg, while five and one subject were outliers due to standing systolic BP <85 mm Hg following tadalafil and placebo, respectively. Severe adverse events potentially related to blood-pressure effects were assessed. No such events were reported following placebo. Two such events were reported following administration of tadalafil. Vertigo was reported in one subject that began 7 hours after dosing and lasted about 5 days. This subject previously experienced a mild episode of vertigo on doxazosin and placebo. Dizziness was reported in another subject that began 25 minutes after dosing and lasted 1 day. No syncope was reported.

In the second doxazosin study, a single oral dose of tadalafil 20 mg was administered to healthy subjects taking oral doxazosin, either 4 or 8 mg daily. The study (N=72 subjects) was conducted in three parts, each a 3-period crossover.

In part A (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 a.m. Tadalafil was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control.

In part B (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 p.m. Tadalafil was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control.

In part C (N=24), subjects were titrated to doxazosin 8 mg administered daily at 8 a.m. In this part, tadalafil or placebo were administered at either 8 a.m. or 8 p.m.

The placebo-subtracted mean maximal decreases in systolic blood pressure over a 12-hour period after dosing in the placebo-controlled portion of the study (part C) are shown in Table 6 and Figure 3.

Table 6: Doxazosin (8 mg/day) Study 2 (Part C): Mean Maximal Decrease in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 20 mg at 8 a.m.	Tadalafil 20 mg at 8 p.m.
Ambulatory Blood-Pressure Monitoring (ABPM)	7	8

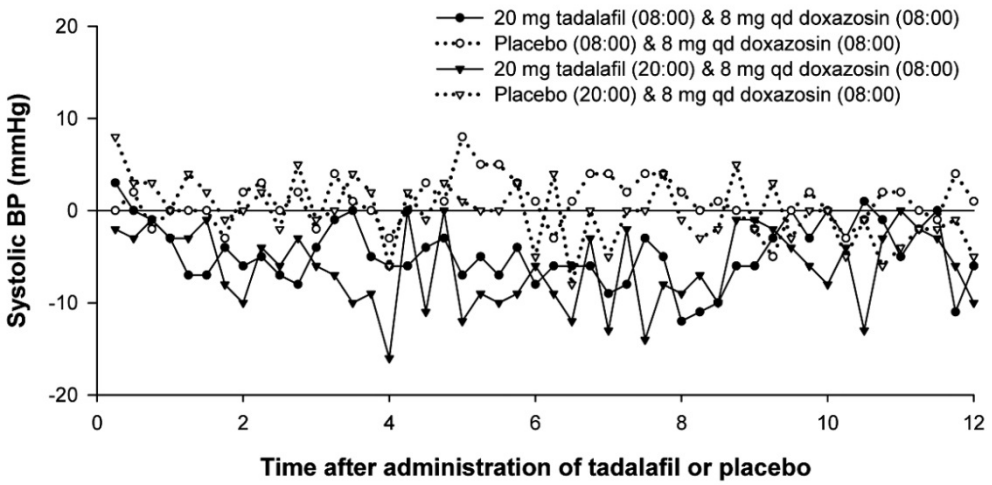


Figure 3: Doxazosin Study 2 (Part C): Mean Change from Time-Matched Baseline in Systolic Blood Pressure

Blood pressure was measured by ABPM every 15 to 30 minutes for up to 36 hours after tadalafil or placebo. Subjects were categorized as outliers if one or more systolic blood pressure readings of <85 mm Hg were recorded or one or more decreases in systolic blood pressure of >30 mm Hg from a time-matched baseline occurred during the analysis interval.

Of the 24 subjects in part C, 16 subjects were categorized as outliers following administration of tadalafil and 6 subjects were categorized as outliers following placebo during the 24-hour period after 8 a.m. dosing of tadalafil or placebo. Of these, 5 and 2 were outliers due to systolic BP <85 mm Hg, while 15 and 4 were outliers due to a decrease from baseline in systolic BP of >30 mm Hg following tadalafil and placebo, respectively.

During the 24-hour period after 8 p.m. dosing, 17 subjects were categorized as outliers following administration of tadalafil and 7 subjects following placebo. Of these, 10 and 2 subjects were outliers due to systolic BP <85 mm Hg, while 15 and 5 subjects were outliers due to a decrease from baseline in systolic BP of >30 mm Hg, following tadalafil and placebo, respectively.

Some additional subjects in both the tadalafil and placebo groups were categorized as outliers in the period beyond 24 hours.

Severe adverse events potentially related to blood-pressure effects were assessed. In the study (N=72 subjects), 2 such events were reported following administration of tadalafil (symptomatic hypotension in one subject that began 10 hours after dosing and lasted approximately 1 hour, and dizziness in another subject that began 11 hours after dosing and lasted 2 minutes). No such events were reported following placebo. In the period prior to tadalafil dosing, one severe event (dizziness) was reported in a subject during the doxazosin run-in phase.

In the third doxazosin study, healthy subjects (N=45 treated; 37 completed) received 28 days of once per day dosing of tadalafil 5 mg or placebo in a two-period crossover design. After 7 days, doxazosin was initiated at 1 mg and titrated up to 4 mg daily over the last 21 days of each period (7 days on 1 mg; 7 days of 2 mg; 7 days of 4 mg doxazosin). The results are shown in Table 7.

Table 7: Doxazosin Study 3: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure		Tadalafil 5 mg
Day 1 of 4 mg Doxazosin	Supine	2.4 (-0.4, 5.2)
	Standing	-0.5 (-4.0, 3.1)
Day 7 of 4 mg Doxazosin	Supine	2.8 (-0.1, 5.7)
	Standing	1.1 (-2.9, 5.0)

Blood pressure was measured manually pre-dose at two time points (-30 and -15 minutes) and then at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours post dose on the first day of each doxazosin dose, (1 mg, 2 mg, 4 mg), as well as on the seventh day of 4 mg doxazosin administration.

Following the first dose of doxazosin 1 mg, there were no outliers on tadalafil 5 mg and one outlier on placebo due to a decrease from baseline in standing systolic BP of >30 mm Hg.

There were 2 outliers on tadalafil 5 mg and none on placebo following the first dose of doxazosin 2 mg due to a decrease from baseline in standing systolic BP of >30 mm Hg.

There were no outliers on tadalafil 5 mg and two on placebo following the first dose of doxazosin 4 mg due to a decrease from baseline in standing systolic BP of >30 mm Hg. There was one outlier on tadalafil 5 mg and three on placebo following the first dose of doxazosin 4 mg due to standing systolic BP <85 mm Hg. Following the seventh day of doxazosin 4 mg, there were no outliers on tadalafil 5 mg, one subject on placebo had a decrease >30 mm Hg in standing systolic blood pressure, and one subject on placebo had standing systolic blood pressure <85 mm Hg. All adverse events potentially related to blood pressure effects were rated as mild or moderate. There were two episodes of syncope in this study, one subject following a dose of tadalafil 5 mg alone, and another subject following coadministration of tadalafil 5 mg and doxazosin 4 mg.

Tamsulosin — In the first tamsulosin study, a single oral dose of tadalafil 10, 20 mg, or placebo was administered in a 3 period, crossover design to healthy subjects taking 0.4 mg once per day tamsulosin, a selective alpha[1A]-adrenergic blocker (N=18 subjects). Tadalafil or placebo was administered 2 hours after tamsulosin following a minimum of seven days of tamsulosin dosing.

Table 8: Tamsulosin (0.4 mg/day) Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 10 mg	Tadalafil 20 mg
Supine	3.2 (-2.3, 8.6)	3.2 (-2.3, 8.7)
Standing	1.7 (-4.7, 8.1)	2.3 (-4.1, 8.7)

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo dosing. There were 2, 2, and 1 outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points) following administration of tadalafil 10 mg, 20 mg, and placebo, respectively. There were no subjects with a standing systolic blood pressure <85 mm Hg. No severe adverse events potentially related to blood-pressure effects were reported. No syncope was reported.

In the second tamsulosin study, healthy subjects (N=39 treated; and 35 completed) received 14 days of once per day dosing of tadalafil 5 mg or placebo in a two-period crossover design. Daily dosing of tamsulosin 0.4 mg was added for the last seven days of each period.

Table 9: Tamsulosin Study 2: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure		Tadalafil 5 mg
Day 1 of 0.4 mg Tamsulosin	Supine	-0.1 (-2.2, 1.9)
	Standing	0.9 (-1.4, 3.2)
Day 7 of 0.4 mg Tamsulosin	Supine	1.2 (-1.2, 3.6)
	Standing	1.2 (-1.0, 3.5)

Blood pressure was measured manually pre-dose at two time points (-30 and -15 minutes) and then at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post dose on the first, sixth and seventh days of tamsulosin administration. There were no outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points). One subject on placebo plus tamsulosin (Day 7) and one subject on tadalafil plus tamsulosin (Day 6) had standing systolic blood pressure <85 mm Hg. No severe adverse events potentially related to blood pressure were reported. No syncope was reported.

Alfuzosin — A single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking once-daily alfuzosin HCl 10 mg extended-release tablets, an alpha[1]-adrenergic blocker (N=17 completed subjects). Tadalafil or placebo was administered 4 hours after alfuzosin following a minimum of seven days of alfuzosin dosing.

Table 10: Alfuzosin (10 mg/day) Study: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 20 mg
Supine	2.2 (-0.9,-5.2)
Standing	4.4 (-0.2, 8.9)

Blood pressure was measured manually at 1, 2, 3, 4, 6, 8, 10, 20, and 24 hours after tadalafil or placebo dosing. There was 1 outlier (subject with a standing systolic blood pressure <85 mm Hg) following administration of tadalafil 20 mg. There were no subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or

more time points. No severe adverse events potentially related to blood pressure effects were reported. No syncope was reported.

Effects on Blood Pressure When Administered with Antihypertensives

Amlodipine — A study was conducted to assess the interaction of amlodipine (5 mg daily) and tadalafil 10 mg. There was no effect of tadalafil on amlodipine blood levels and no effect of amlodipine on tadalafil blood levels. The mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking amlodipine was 3/2 mm Hg, compared to placebo. In a similar study using tadalafil 20 mg, there were no clinically significant differences between tadalafil and placebo in subjects taking amlodipine.

Angiotensin II receptor blockers (with and without other antihypertensives) — A study was conducted to assess the interaction of angiotensin II receptor blockers and tadalafil 20 mg. Subjects in the study were taking any marketed angiotensin II receptor blocker, either alone, as a component of a combination product, or as part of a multiple antihypertensive regimen. Following dosing, ambulatory measurements of blood pressure revealed differences between tadalafil and placebo of 8/4 mm Hg in systolic/diastolic blood pressure.

Bendrofluazide — A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking bendrofluazide was 6/4 mm Hg, compared to placebo.

Enalapril — A study was conducted to assess the interaction of enalapril (10 to 20 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking enalapril was 4/1 mm Hg, compared to placebo.

Metoprolol — A study was conducted to assess the interaction of sustained-release metoprolol (25 to 200 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking metoprolol was 5/3 mm Hg, compared to placebo.

Effects on Blood Pressure When Administered with Alcohol

Alcohol and PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. The interaction of tadalafil with alcohol was evaluated in 3 clinical pharmacology studies. In 2 of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately 6 ounces of 80-proof vodka in an 80-kg male, and tadalafil was administered at a dose of 10 mg in one study and 20 mg in another. In both these studies, all patients imbibed the entire alcohol dose within 10 minutes of starting. In one of these two studies, blood alcohol levels of 0.08% were confirmed. In these two studies, more patients had clinically significant decreases in blood pressure on the combination of tadalafil and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When tadalafil 20 mg was administered with a lower dose of alcohol (0.6 g/kg, which is equivalent to approximately 4 ounces of 80-proof vodka, administered in less than 10 minutes), orthostatic hypotension was not observed, dizziness occurred with similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated.

Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Effects on Exercise Stress Testing

The effects of tadalafil on cardiac function, hemodynamics, and exercise tolerance were investigated in a single clinical pharmacology study. In this blinded crossover trial, 23 subjects with stable coronary artery disease and evidence of exercise-induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time was 3 seconds (tadalafil 10 mg minus placebo), which represented no clinically meaningful difference. Further statistical analysis demonstrated that tadalafil was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some subjects who received tadalafil followed by sublingual nitroglycerin in the post-exercise period, clinically significant reductions in blood pressure were observed, consistent with the augmentation by tadalafil of the blood-pressure-lowering effects of nitrates.

Effects on Vision

Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupilometry. Across all clinical studies with CIALIS, reports of changes in color vision were rare (<0.1% of patients).

Effects on Sperm Characteristics

Three studies were conducted in men to assess the potential effect on sperm characteristics of tadalafil 10 mg (one 6 month study) and 20 mg (one 6 month and one 9 month study) administered daily. There were no adverse effects on sperm morphology or sperm motility in any of the three studies. In the study of 10 mg tadalafil for 6 months and the

study of 20 mg tadalafil for 9 months, results showed a decrease in mean sperm concentrations relative to placebo, although these differences were not clinically meaningful. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. In addition there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20 mg of tadalafil compared to placebo.

Effects on Cardiac Electrophysiology

The effect of a single 100-mg dose of tadalafil on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blinded, placebo, and active (intravenous ibutilide) -controlled crossover study in 90 healthy males aged 18 to 53 years. The mean change in QT_c (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (two-sided 90% CI=1.9, 5.1). The mean change in QT_c (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (two-sided 90% CI=1.2, 4.4). A 100-mg dose of tadalafil (5 times the highest recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with potent CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100-mg dose of tadalafil compared to placebo was 3.1 beats per minute.

12.3 Pharmacokinetics

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once per day dosing and exposure is approximately 1.6-fold greater than after a single dose. Mean tadalafil concentrations measured after the administration of a single oral dose of 20 mg and single and once daily multiple doses of 5 mg, from a separate study, (*see* Figure 4) to healthy male subjects are depicted in Figure 4.

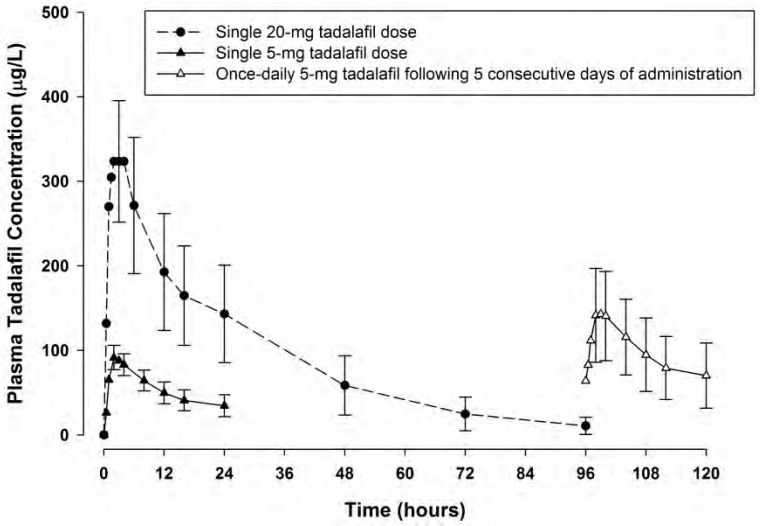


Figure 4: Plasma tadalafil concentrations (mean ± SD) following a single 20-mg tadalafil dose and single and once daily multiple doses of 5 mg

Absorption — After single oral-dose administration, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food; thus CIALIS may be taken with or without food.

Distribution — The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism — Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. *In vitro* data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Excretion — The mean oral clearance for tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Geriatric — Healthy male elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered *[see Use in Specific Populations (8.5)]*.

Patients with Diabetes Mellitus — In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

Patients with BPH — In patients with BPH following single and multiple-doses of 20 mg tadalafil, no statistically significant differences in exposure (AUC and C_{max}) were observed between elderly (70 to 85 years) and younger (≤60 years of age) subjects. No dose adjustment is warranted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Tadalafil was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 400 mg/kg/day. Systemic drug exposures, as measured by AUC of unbound tadalafil, were approximately 10-fold for mice, and 14- and 26-fold for male and female rats, respectively, the exposures in human males given Maximum Recommended Human Dose (MRHD) of 20 mg.

Mutagenesis — Tadalafil was not mutagenic in the *in vitro* bacterial Ames assays or the forward mutation test in mouse lymphoma cells. Tadalafil was not clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes or the *in vivo* rat micronucleus assays.

Impairment of Fertility — There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day, a dose producing AUCs for unbound tadalafil of 14-fold for males or 26-fold for females the exposures observed in human males given the MRHD of 20 mg. In beagle dogs given tadalafil daily for 3 to 12 months, there was treatment-related non-reversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20-100% of the dogs that resulted in a decrease in spermatogenesis in 40-75% of the dogs at doses of ≥10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect-level (NOAEL) (10 mg/kg/day) for unbound tadalafil was similar to that expected in humans at the MRHD of 20 mg.

There were no treatment-related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

13.2 Animal Toxicology and/or Pharmacology

Animal studies showed vascular inflammation in tadalafil-treated mice, rats, and dogs. In mice and rats, lymphoid necrosis and hemorrhage were seen in the spleen, thymus, and mesenteric lymph nodes at unbound tadalafil exposure of 2- to 33-fold above the human exposure (AUCs) at the MRHD of 20 mg. In dogs, an increased incidence of disseminated arteritis was observed in 1- and 6-month studies at unbound tadalafil exposure of 1- to 54-fold above the human exposure (AUC) at the MRHD of 20 mg. In a 12-month dog study, no disseminated arteritis was observed, but 2 dogs exhibited marked decreases in white blood cells (neutrophils) and moderate decreases in platelets with inflammatory signs at unbound tadalafil exposures of approximately 14- to 18-fold the human exposure at the MRHD of 20 mg. The abnormal blood-cell findings were reversible within 2 weeks after stopping treatment.

14 CLINICAL STUDIES

14.1 CIALIS for Use as Needed for ED

The efficacy and safety of tadalafil in the treatment of erectile dysfunction has been evaluated in 22 clinical trials of up to 24-weeks duration, involving over 4000 patients. CIALIS, when taken as needed up to once per day, was shown to be effective in improving erectile function in men with erectile dysfunction (ED).

CIALIS was studied in the general ED population in 7 randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design, primary efficacy and safety studies of 12-weeks duration. Two of these studies were conducted in the United States and 5 were conducted in centers outside the US. Additional efficacy and safety studies were performed in ED patients with diabetes mellitus and in patients who developed ED status post bilateral nerve-sparing radical prostatectomy.

In these 7 trials, CIALIS was taken as needed, at doses ranging from 2.5 to 20 mg, up to once per day. Patients were free to choose the time interval between dose administration and the time of sexual attempts. Food and alcohol intake were not restricted.

Several assessment tools were used to evaluate the effect of CIALIS on erectile function. The 3 primary outcome measures were the Erectile Function (EF) domain of the International Index of Erectile Function (IIEF) and Questions 2 and 3 from Sexual Encounter Profile (SEP). The IIEF is a 4-week recall questionnaire that was administered at the end of a treatment-free baseline period and subsequently at follow-up visits after randomization. The IIEF EF domain has a 30-point total score, where higher scores reflect better erectile function. SEP is a diary in which patients recorded each sexual attempt made throughout the study. SEP Question 2 asks, “Were you able to insert your penis into the partner’s vagina?” SEP Question 3 asks, “Did your erection last long enough for you to have successful intercourse?” The overall

percentage of successful attempts to insert the penis into the vagina (SEP2) and to maintain the erection for successful intercourse (SEP3) is derived for each patient.

Results in ED Population in US Trials — The 2 primary US efficacy and safety trials included a total of 402 men with erectile dysfunction, with a mean age of 59 years (range 27 to 87 years). The population was 78% White, 14% Black, 7% Hispanic, and 1% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (>90%) patients reported ED of at least 1-year duration. Study A was conducted primarily in academic centers. Study B was conducted primarily in community-based urology practices. In each of these 2 trials, CIALIS 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (*see* Table 11). The treatment effect of CIALIS did not diminish over time.

Table 11: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in the Two Primary US Trials

	Study A			Study B		
	Placebo (N=49)	CIALIS 20 mg (N=146)	p-value	Placebo (N=48)	CIALIS 20 mg (N=159)	p-value
EF Domain Score						
Endpoint	13.5	19.5		13.6	22.5	
Change from baseline	-0.2	6.9	<.001	0.3	9.3	<.001
Insertion of Penis (SEP2)						
Endpoint	39%	62%		43%	77%	
Change from baseline	2%	26%	<.001	2%	32%	<.001
Maintenance of Erection (SEP3)						
Endpoint	25%	50%		23%	64%	
Change from baseline	5%	34%	<.001	4%	44%	<.001

Results in General ED Population in Trials Outside the US — The 5 primary efficacy and safety studies conducted in the general ED population outside the US included 1112 patients, with a mean age of 59 years (range 21 to 82 years). The population was 76% White, 1% Black, 3% Hispanic, and 20% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (90%) patients reported ED of at least 1-year duration. In these 5 trials, CIALIS 5, 10, and 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (*see* Tables 12, 13 and 14). The treatment effect of CIALIS did not diminish over time.

Table 12: Mean Endpoint and Change from Baseline for the EF Domain of the IIEF in the General ED Population in Five Primary Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	15.0 [0.7]	17.9 [4.0]	20.0 [5.6]	
		p=.006	*p<.001*	
Study D				
Endpoint [Change from baseline]	14.4 [1.1]	17.5 [5.1]	20.6 [6.0]	
		p=.002	*p<.001*	
Study E				
Endpoint [Change from baseline]	18.1 [2.6]		22.6 [8.1]	25.0 [8.0]
			p<.001	*p<.001*
Study F[a]				
Endpoint [Change from baseline]	12.7 [-1.6]			22.8 [6.8]
				p<.001
Study G				
Endpoint [Change from baseline]	14.5 [-0.9]		21.2 [6.6]	23.3 [8.0]
			p<.001	*p<.001*

[a] Treatment duration in Study F was 6 months

Table 13: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 2 ("Were you able to insert your penis into the partner's vagina?") in the General ED Population in Five Pivotal Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	49% [6%]	57% [15%]	73% [29%]	
		p=.063	*p<.001*	
Study D				
Endpoint [Change from baseline]	46% [2%]	56% [18%]	68% [15%]	
		p=.008	*p<.001*	
Study E				
Endpoint [Change from baseline]	55% [10%]		77% [35%]	85% [35%]
			p<.001	*p<.001*
Study F[a]				
Endpoint [Change from baseline]	42% [-8%]			81% [27%]
				p<.001
Study G				
Endpoint [Change from baseline]	45% [-6%]		73% [21%]	76% [21%]
			p<.001	*p<.001*

[a] Treatment duration in Study F was 6 months

Table 14: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 3 ("Did your erection last long enough for you to have successful intercourse?") in the General ED Population in Five Pivotal Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	26% [4%]	38% [19%]	58% [32%]	
		p=.040	*p<.001*	
Study D				
Endpoint [Change from baseline]	28% [4%]	42% [24%]	51% [26%]	
		p<.001	*p<.001*	
Study E				
Endpoint [Change from baseline]	43% [15%]		70% [48%]	78% [50%]
			p<.001	*p<.001*
Study F[a]				
Endpoint [Change from baseline]	27% [1%]			74% [40%]
				p<.001
Study G				
Endpoint [Change from baseline]	32% [5%]		57% [33%]	62% [29%]
			p<.001	*p<.001*

[a] Treatment duration in Study F was 6 months

In addition, there were improvements in EF domain scores, success rates based upon SEP Questions 2 and 3, and patient-reported improvement in erections across patients with ED of all degrees of disease severity while taking CIALIS, compared to patients on placebo.

Therefore, in all 7 primary efficacy and safety studies, CIALIS showed statistically significant improvement in patients' ability to achieve an erection sufficient for vaginal penetration and to maintain the erection long enough for successful intercourse, as measured by the IIEF questionnaire and by SEP diaries.

Efficacy Results in ED Patients with Diabetes Mellitus — CIALIS was shown to be effective in treating ED in patients with diabetes mellitus. Patients with diabetes were included in all 7 primary efficacy studies in the general ED population (N=235) and in one study that specifically assessed CIALIS in ED patients with type 1 or type 2 diabetes (N=216). In this randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 15).

Table 15: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in ED Patients with Diabetes

	Placebo	CIALIS 10 mg	CIALIS 20 mg	
	(N=71)	(N=73)	(N=72)	p-value
EF Domain Score				
Endpoint [Change from baseline]	12.2 [0.1]	19.3 [6.4]	18.7 [7.3]	<.001
Insertion of Penis (SEP2)				
Endpoint [Change from baseline]	30% [-4%]	57% [22%]	54% [23%]	<.001
Maintenance of Erection (SEP3)				
Endpoint [Change from baseline]	20% [2%]	48% [28%]	42% [29%]	<.001

Efficacy Results in ED Patients following Radical Prostatectomy — CIALIS was shown to be effective in treating patients who developed ED following bilateral nerve-sparing radical prostatectomy. In 1 randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial in this population (N=303), CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 16).

Table 16: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in Patients who Developed ED Following Bilateral Nerve-Sparing Radical Prostatectomy

	Placebo	CIALIS 20 mg	
	(N=102)	(N=201)	p-value
EF Domain Score			
Endpoint [Change from baseline]	13.3 [1.1]	17.7 [5.3]	<.001
Insertion of Penis (SEP2)			
Endpoint [Change from baseline]	32% [2%]	54% [22%]	<.001
Maintenance of Erection (SEP3)			
Endpoint [Change from baseline]	19% [4%]	41% [23%]	<.001

Results in Studies to Determine the Optimal Use of CIALIS — Several studies were conducted with the objective of determining the optimal use of CIALIS in the treatment of ED. In one of these studies, the percentage of patients reporting successful erections within 30 minutes of dosing was determined. In this randomized, placebo-controlled, double-blinded trial, 223 patients were randomized to placebo, CIALIS 10, or 20 mg. Using a stopwatch, patients recorded the time following dosing at which a successful erection was obtained. A successful erection was defined as at least 1 erection in 4 attempts that led to successful intercourse. At or prior to 30 minutes, 35% (26/74), 38% (28/74), and 52% (39/75) of patients in the placebo, 10-, and 20-mg groups, respectively, reported successful erections as defined above.

Two studies were conducted to assess the efficacy of CIALIS at a given timepoint after dosing, specifically at 24 hours and at 36 hours after dosing.

In the first of these studies, 348 patients with ED were randomized to placebo or CIALIS 20 mg. Patients were encouraged to make 4 total attempts at intercourse; 2 attempts were to occur at 24 hours after dosing and 2 completely separate attempts were to occur at 36 hours after dosing. The results demonstrated a difference between the placebo group and the CIALIS group at each of the pre-specified timepoints. At the 24-hour timepoint, (more specifically, 22 to 26 hours), 53/144 (37%) patients reported at least 1 successful intercourse in the placebo group versus 84/138 (61%) in the CIALIS 20-mg group. At the 36-hour timepoint (more specifically, 33 to 39 hours), 49/133 (37%) of patients reported at least 1 successful intercourse in the placebo group versus 88/137 (64%) in the CIALIS 20-mg group.

In the second of these studies, a total of 483 patients were evenly randomized to 1 of 6 groups: 3 different dosing groups (placebo, CIALIS 10, or 20 mg) that were instructed to attempt intercourse at 2 different times (24 and 36 hours post-dosing). Patients were encouraged to make 4 separate attempts at their assigned dose and assigned timepoint. In this study, the results demonstrated a statistically significant difference between the placebo group and the CIALIS groups at each of the pre-specified timepoints. At the 24-hour timepoint, the mean, per patient percentage of attempts resulting in successful intercourse were 42, 56, and 67% for the placebo, CIALIS 10-, and 20-mg groups, respectively. At the 36-hour timepoint, the mean, per-patient percentage of attempts resulting in successful intercourse were 33, 56, and 62% for placebo, CIALIS 10-, and 20-mg groups, respectively.

14.2 CIALIS for Once Daily Use for ED

The efficacy and safety of CIALIS for once daily use in the treatment of erectile dysfunction has been evaluated in 2 clinical trials of 12-weeks duration and 1 clinical trial of 24-weeks duration, involving a total of 853 patients. CIALIS, when taken once daily, was shown to be effective in improving erectile function in men with erectile dysfunction (ED).

CIALIS was studied in the general ED population in 2 randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design, primary efficacy and safety studies of 12- and 24-weeks duration, respectively. One of these studies was conducted in the United States and one was conducted in centers outside the US. An additional efficacy and safety study was performed in ED patients with diabetes mellitus. CIALIS was taken once daily at doses ranging from 2.5 to 10 mg. Food and alcohol intake were not restricted. Timing of sexual activity was not restricted relative to when patients took Cialis.

Results in General ED Population — The primary US efficacy and safety trial included a total of 287 patients, with a mean age of 59 years (range 25 to 82 years). The population was 86% White, 6% Black, 6% Hispanic, and 2% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (>96%) patients reported ED of at least 1-year duration.

The primary efficacy and safety study conducted outside the US included 268 patients, with a mean age of 56 years (range 21 to 78 years). The population was 86% White, 3% Black, 0.4% Hispanic, and 10% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Ninety-three percent of patients reported ED of at least 1-year duration.

In each of these trials, conducted without regard to the timing of dose and sexual intercourse, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 17). When taken as directed, CIALIS was effective at improving erectile function.

In the 6 month double-blind study, the treatment effect of CIALIS did not diminish over time.

Table 17: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in the Two CIALIS for Once Daily Use Studies

	Study H[a]				Study I[b]		
	Placebo	CIALIS 2.5 mg	CIALIS 5 mg		Placebo	CIALIS 5 mg	
	(N=94)	(N=96)	(N=97)	p-value	(N=54)	(N=109)	p-value
EF Domain Score							
Endpoint	14.6	19.1	20.8		15.0	22.8	
Change from baseline	1.2	6.1[c]	7.0[c]	<.001	0.9	9.7[c]	<.001
Insertion of Penis (SEP2)							
Endpoint	51%	65%	71%		52%	79%	
Change from baseline	5%	24%[c]	26%[c]	<.001	11%	37%[c]	<.001
Maintenance of Erection (SEP3)							
Endpoint	31%	50%	57%		37%	67%	
Change from baseline	10%	31%[c]	35%[c]	<.001	13%	46%[c]	<.001

[a] Twenty-four-week study conducted in the US.

[b] Twelve-week study conducted outside the US.

[c] Statistically significantly different from placebo.

Efficacy Results in ED Patients with Diabetes Mellitus — CIALIS for once daily use was shown to be effective in treating ED in patients with diabetes mellitus. Patients with diabetes were included in both studies in the general ED population (N=79). A third randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design trial included only ED patients with type 1 or type 2 diabetes (N=298). In this third trial, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 18).

Table 18: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a CIALIS for Once Daily Use Study in ED Patients with Diabetes

	Placebo	CIALIS 2.5 mg	CIALIS 5 mg	
	(N=100)	(N=100)	(N=98)	p-value
EF Domain Score				
Endpoint	14.7	18.3	17.2	
Change from baseline	1.3	4.8[a]	4.5[a]	<.001
Insertion of Penis (SEP2)				
Endpoint	43%	62%	61%	

Change from baseline	5%	21%[a]	29%[a]	<.001
Maintenance of Erection (SEP3)				
Endpoint	28%	46%	41%	
Change from baseline	8%	26%[a]	25%[a]	<.001

[a] Statistically significantly different from placebo.

14.3 CIALIS 5 mg for Once Daily Use for Benign Prostatic Hyperplasia (BPH)

The efficacy and safety of CIALIS for once daily use for the treatment of the signs and symptoms of BPH was evaluated in 3 randomized, multinational, double-blinded, placebo-controlled, parallel-design, efficacy and safety studies of 12 weeks duration. Two of these studies were in men with BPH and one study was specific to men with both ED and BPH *[see Clinical Studies (14.4)]*. The first study (Study J) randomized 1058 patients to receive either CIALIS 2.5 mg, 5 mg, 10 mg or 20 mg for once daily use or placebo. The second study (Study K) randomized 325 patients to receive either CIALIS 5 mg for once daily use or placebo. The full study population was 87% White, 2% Black, 11% other races; 15% was of Hispanic ethnicity. Patients with multiple co-morbid conditions such as diabetes mellitus, hypertension, and other cardiovascular disease were included.

The primary efficacy endpoint in the two studies that evaluated the effect of CIALIS for the signs and symptoms of BPH was the International Prostate Symptom Score (IPSS), a four week recall questionnaire that was administered at the beginning and end of a placebo run-in period and subsequently at follow-up visits after randomization. The IPSS assesses the severity of irritative (frequency, urgency, nocturia) and obstructive symptoms (incomplete emptying, stopping and starting, weak stream, and pushing or straining), with scores ranging from 0 to 35; higher numeric scores representing greater severity. Maximum urinary flow rate (Q_{max}), an objective measure of urine flow, was assessed as a secondary efficacy endpoint in Study J and as a safety endpoint in Study K.

The results for BPH patients with moderate to severe symptoms and a mean age of 63.2 years (range 44 to 87) who received either CIALIS 5 mg for once daily use or placebo (N=748) in Studies J and K are shown in Table 19 and Figures 5 and 6, respectively.

In each of these 2 trials, CIALIS 5 mg for once daily use resulted in statistically significant improvement in the total IPSS compared to placebo. Mean total IPSS showed a decrease starting at the first scheduled observation (4 weeks) in Study K and remained decreased through 12 weeks.

Table 19: Mean IPSS Changes in BPH Patients in Two CIALIS for Once Daily Use Studies

	Study J			Study K		
	Placebo (N=205)	CIALIS 5 mg (N=205)	p-value	Placebo (N=164)	CIALIS 5 mg (N=160)	p-value
Total Symptom Score (IPSS)						
Baseline	17.1	17.3		16.6	17.1	
Change from Baseline to Week 12	-2.2	-4.8	<.001	-3.6	-5.6	.004

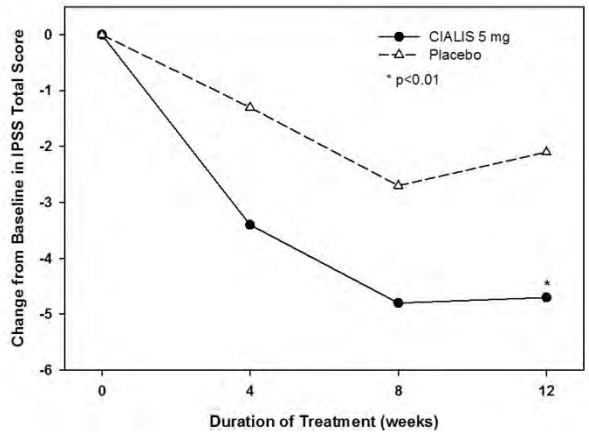


Figure 5: Mean IPSS Changes in BPH Patients by Visit in Study J

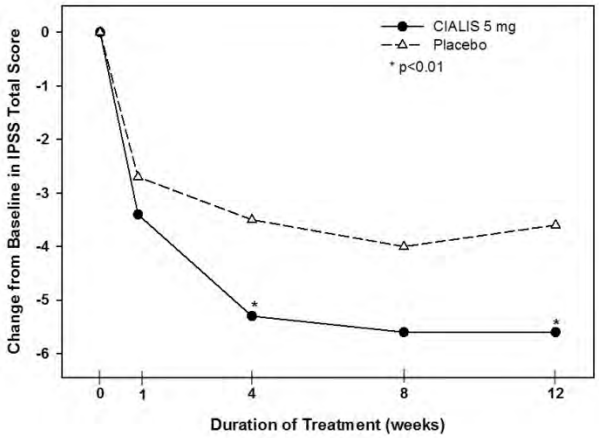


Figure 6: Mean IPSS Changes in BPH Patients by Visit in Study K

In Study J, the effect of CIALIS 5 mg once daily on maximum urinary flow rate (Q_{max}) was evaluated as a secondary efficacy endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

In Study K, the effect of CIALIS 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.1 mL/sec); however, these changes were not significantly different between groups.

Efficacy Results in Patients with BPH initiating CIALIS and Finasteride – CIALIS for once daily use initiated together with finasteride was shown to be effective in treating the signs and symptoms of BPH in men with an enlarged prostate (>30 cc) for up to 26 weeks. This additional double-blinded, parallel-design study of 26 weeks duration randomized 696 men to initiate either CIALIS 5 mg with finasteride 5 mg or placebo with finasteride 5 mg. The study population had a mean age of 64 years (range 46-86). Patients with multiple co-morbid conditions such as erectile dysfunction, diabetes mellitus, hypertension, and other cardiovascular disease were included.

CIALIS with finasteride demonstrated statistically significant improvement in the signs and symptoms of BPH compared to placebo with finasteride, as measured by the total IPSS at 12 weeks, the primary study endpoint (*see* Table 20). Key secondary endpoints demonstrated improvement in total IPSS starting at the first scheduled observation at week 4 (CIALIS -4.0, placebo -2.3: p<.001) and the score remained decreased through 26 weeks (CIALIS -5.5, placebo -4.5; p=.022). However, the magnitude of the treatment difference between placebo/finasteride and CIALIS/finasteride decreased from 1.7 points at Week 4 to 1.0 point at Week 26, as shown in Table 20 and in Figure 7. The incremental benefit of CIALIS beyond 26 weeks is unknown.

Table 20: Mean Total IPSS Changes in BPH Patients in a CIALIS for Once Daily Use Study Together with Finasteride

		Placebo and finasteride 5 mg		CIALIS 5mg and finasteride 5 mg	Treatment difference	
	n	(N=350)[a]	n	(N=345)[a]		p-value[b]
Total Symptom Score (IPSS)						
Baseline[c]	349	17.4	344	17.1		
Change from Baseline to Week 4[b]	340	-2.3	330	-4.0	-1.7	<.001
Change from Baseline to Week 12[b]	318	-3.8	317	-5.2	-1.4	.001
Change from Baseline to Week 26[b]	295	-4.5	308	-5.5	-1.0	.022

[a] Overall ITT population.

[b] Mixed model for repeated measurements.

[c] Unadjusted mean.

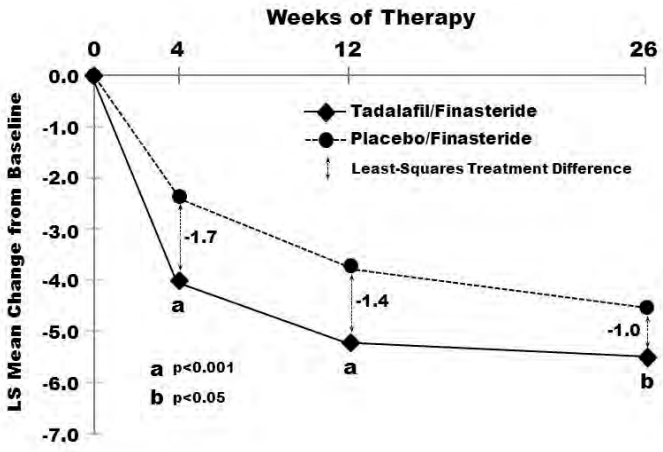


Figure 7: Mean Total IPSS Changes By Visit in BPH Patients Taking CIALIS for Once Daily Use Together With Finasteride

In the 404 patients who had both ED and BPH at baseline, changes in erectile function were assessed as key secondary endpoints using the EF domain of the IIEF questionnaire. CIALIS with finasteride (N=203) was compared to placebo with finasteride (N=201). A statistically significant improvement from baseline (CIALIS/finasteride 13.7, placebo/finasteride 15.1) was observed at week 4 (CIALIS/finasteride 3.7, placebo/finasteride -1.1; p<.001), week 12 (CIALIS/finasteride 4.7, placebo/finasteride 0.6; p<.001), and week 26 (CIALIS/finasteride 4.7, placebo/finasteride 0.0; p<.001).

14.4 CIALIS 5 mg for Once Daily Use for ED and BPH

The efficacy and safety of CIALIS for once daily use for the treatment of ED, and the signs and symptoms of BPH, in patients with both conditions was evaluated in one placebo-controlled, multinational, double-blind, parallel-arm study which randomized 606 patients to receive either CIALIS 2.5 mg, 5 mg, for once daily use or placebo. ED severity ranged from mild to severe and BPH severity ranged from moderate to severe. The full study population had a mean age of 63 years (range 45 to 83) and was 93% White, 4% Black, 3% other races; 16% were of Hispanic ethnicity. Patients with multiple co-morbid conditions such as diabetes mellitus, hypertension, and other cardiovascular disease were included.

In this study, the co-primary endpoints were total IPSS and the Erectile Function (EF) domain score of the International Index of Erectile Function (IIEF). One of the key secondary endpoints in this study was Question 3 of the Sexual Encounter Profile diary (SEP3). Timing of sexual activity was not restricted relative to when patients took CIALIS.

The efficacy results for patients with both ED and BPH, who received either CIALIS 5 mg for once daily use or placebo (N=408) are shown in Tables 21 and 22 and Figure 8.

CIALIS 5 mg for once daily use resulted in statistically significant improvements in the total IPSS and in the EF domain of the IIEF questionnaire. CIALIS 5 mg for once daily use also resulted in statistically significant improvement in SEP3. CIALIS 2.5 mg did not result in statistically significant improvement in the total IPSS.

Table 21: Mean IPSS and IIEF EF Domain Changes in the CIALIS 5 mg for Once Daily Use Study in Patients with ED and BPH

	Placebo	CIALIS 5 mg	p-value
Total Symptom Score (IPSS)			
	(N=193)	**(N=206)**	
Baseline	18.2	18.5	
Change from Baseline to Week 12	-3.8	-6.1	<.001
EF Domain Score (IIEF EF)			
	(N=188)	**(N=202)**	
Baseline	15.6	16.5	
Endpoint	17.6	22.9	
Change from Baseline to Week 12	1.9	6.5	<.001

Table 22: Mean SEP Question 3 Changes in the CIALIS 5 mg for Once Daily Use Study in Patients with ED and BPH

	Placebo (N=187)	CIALIS 5 mg (N=199)	p-value
Maintenance of Erection (SEP3)			
Baseline	36%	43%	
Endpoint	48%	72%	
Change from Baseline to Week 12	12%	32%	<.001

CIALIS for once daily use resulted in improvement in the IPSS total score at the first scheduled observation (week 2) and throughout the 12 weeks of treatment (*see* Figure 8).

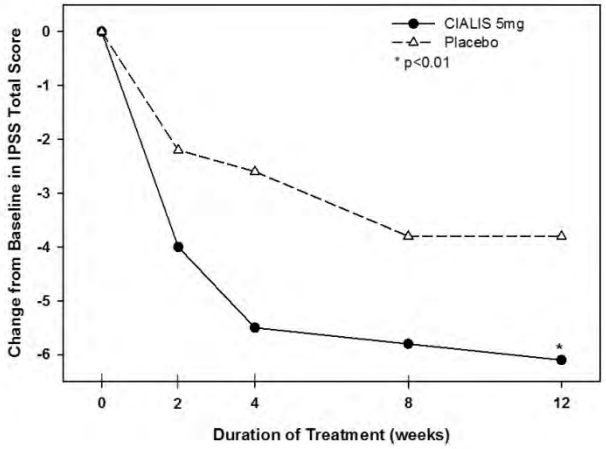


Figure 8: Mean IPSS Changes in ED/BPH Patients by Visit in Study L

In this study, the effect of CIALIS 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CIALIS (tadalafil) is supplied as follows:

Four strengths of almond-shaped tablets are available in different sizes and different shades of yellow, and supplied in the following package sizes:

2.5 mg tablets debossed with “C 2 1/2”
Blisters of 2 x 15 NDC 0002-4465-34
5 mg tablets debossed with “C 5”
Bottles of 30 NDC 0002-4462-30
Blisters of 2 x 15 NDC 0002-4462-34
10 mg tablets debossed with “C 10”
Bottles of 30 NDC 0002-4463-30
20 mg tablets debossed with “C 20”
Bottles of 30 NDC 0002-4464-30

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

“See FDA-approved patient labeling (Patient Information)”

17.1 Nitrates

Physicians should discuss with patients the contraindication of CIALIS with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of CIALIS with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of CIALIS. In such a patient, who has taken CIALIS, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking CIALIS should seek immediate medical attention *[see Contraindications (4.1) and Warnings and Precautions (5.1)]*.

17.2 Guanylate Cyclase (GC) Stimulators

Physicians should discuss with patients the contraindication of CIALIS with any use of a GC stimulator, such as riociguat, for pulmonary arterial hypertension. Patients should be counseled that the concomitant use of CIALIS with GC stimulators may cause blood pressure to drop to an unsafe level.

17.3 Cardiovascular Considerations

Physicians should consider the potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Physicians should advise patients who experience symptoms upon initiation of sexual activity to refrain from further sexual activity and seek immediate medical attention *[see Warnings and Precautions (5.1)]*.

17.4 Concomitant Use with Drugs Which Lower Blood Pressure

Physicians should discuss with patients the potential for CIALIS to augment the blood-pressure-lowering effect of alpha-blockers, and antihypertensive medications *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

17.5 Potential for Drug Interactions When Taking CIALIS for Once Daily Use

Physicians should discuss with patients the clinical implications of continuous exposure to tadalafil when prescribing CIALIS for once daily use, especially the potential for interactions with medications (e.g., nitrates, alpha-blockers, antihypertensives and potent inhibitors of cytochrome P450 3A4) and with substantial consumption of alcohol. *[see Dosage and Administration (2.7), Warnings and Precautions (5.6), Drug Interactions (7.1, 7.2), Clinical Pharmacology (12.2), and Clinical Studies (14.2)]*.

17.6 Priapism

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Physicians should advise patients who have an erection lasting greater than 4 hours, whether painful or not, to seek emergency medical attention.

17.7 Sudden Loss of Vision

Physicians should advise patients to stop use of all PDE5 inhibitors, including CIALIS, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including possible permanent loss of vision, that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. Physicians should discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye. Physicians should also discuss with patients the increased risk of NAION among the general population in patients with a “crowded” optic disc, although evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including CIALIS, for this uncommon condition *[see Warnings and Precautions (5.4) and Adverse Reactions (6.2)]*.

17.8 Sudden Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including CIALIS, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including CIALIS. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6.1, 6.2)]*.

17.9 Alcohol

Patients should be made aware that both alcohol and CIALIS, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *[see Warnings and Precautions (5.9), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

17.10 Sexually Transmitted Disease

The use of CIALIS offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

17.11 Recommended Administration

Physicians should instruct patients on the appropriate administration of CIALIS to allow optimal use.

For CIALIS for use as needed in men with ED, patients should be instructed to take one tablet at least 30 minutes before anticipated sexual activity. In most patients, the ability to have sexual intercourse is improved for up to 36 hours.

For CIALIS for once daily use in men with ED or ED/BPH, patients should be instructed to take one tablet at approximately the same time every day without regard for the timing of sexual activity. Cialis is effective at improving erectile function over the course of therapy.

For CIALIS for once daily use in men with BPH, patients should be instructed to take one tablet at approximately the same time every day.

Revision Date: MM/YYYY

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA

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CLS-A2.01-NL0003-USPI-YYYYMMDD

LVDR:TEAE by Decreasing Frequency to ≥2% in IC351-Treated Patients

Event Classification	IC351 (N = 331)	
	n	%
	144	43.5
Headache	39	11.8
Dyspepsia	35	10.6
Rhinitis	24	7.3
Vasodilatation	17	5.1
Pharyngitis	15	4.5
Back pain	12	3.6
Pain	12	3.6
Surgical procedure	12	3.6
Diarrhea	10	3.0
Dizziness	8	2.4

9.5.5.8.2 DISCONTINUATIONS DUE TO ADVERSE EVENTS

There were a total of 19 discontinuations . 9 were due to serious AE's. serious event included a case of vitrous detachment.

9.5.5.8.3 SERIOUS ADVERSE EVENTS

Fourteen patients experienced serious adverse events in this study. No deaths occurred in this study. None of the serious adverse events, in the opinion of the investigator, was considered to be related to the study drug or protocol procedures. Patients 004-1169, 004-1173, and 504-5240 discontinued from the study due to serious adverse events. Table 49 lists the serious adverse events reported during this study.

Table 48: LVDR: Serious Adverse Events: Serious Adverse Events: All Randomized Patients

Medical Officer's Comments:

1. These three open-label studies provide information on the safety and tolerability of IC351 administered long-term.
2. The serious adverse events were mostly unrelated to the study drug. In the popuation studied, the mycardial infarctions and cereberovascular events were related to preexisting condition and the incidence of the events were comparable to the population at large.
3. Of 6 deaths reported, none could be clearly attributed to the study drug.
4. Of note were the discontinuation due to headaches and dyspepsia reported on increased dosing. This further reinforces the concept of 10mg dose as a first option to the patients.
5. The most frequently reported adverse events were headache, dyspepsia, back

pain, infection, and flu syndrome. Myalgia, rhinitis (nasal congestion), and vasodilatation (flushing) were reported less frequently.

6. There were no clinically significant laboratory abnormalities attributable to IC351.

9.5.6 Special Safety Considerations :

9.5.6 .1 EFFECTS OF IC351 ON BLOOD PRESSURE AND HEART RATE:

In the primary placebo-controlled phase 3 integrated database, the mean changes from baseline to endpoint for blood pressure in patients treated with IC351 were not statistically different from those seen in patients treated with placebo. When adverse events were analyzed in patients with and without hypertension treated with either IC351 or placebo, there were no significant differences between the groups.
In the clinical pharmacology populations studied, the effect of IC351 on vital signs in normotensive and hypertensive subjects was independent of dose and of no clinical significance . There were no clinically significant decreases in blood pressure when IC351 was administered alone or co-administered with anti hypertensive medications.

Medical Officers Comments:

The data was reviewed .The above mentioned hemodynamic alterations, did not produce a clinically significant event.

9.5.6.2 PHARMACODYNAMIC INTERACTIONS WITH ANTIHYPERTENSIVE AGENTS

The reader is referred to clinical pharmacology section and a formal review of Drug – Drug interactions.
The potential of IC351 to augment the hypotensive effects of all major antihypertensive classes were examined, including a calcium channel blocker (amlodipine. LVAV and LVDP), an ACE inhibitor (enalapril,.LVBC), a beta blocker (metoprolol, LVAW), a thiazide diuretic (bendrofluazide,.LVAX), an angiotensin II receptor antagonist (any type and dose, combination with thiazide acceptable,.LVDS), and an alpha 1 adrenergic antagonist (tamsulosin,.LVAY).
The primary parameters assessed in all of these studies included systolic blood pressure, diastolic blood pressure, and heart rate, all of which were measured intermittently over a period of at least 12 hours after IC351 administration. These studies indicate that there was no clinically significant interaction between IC351 and any of the classes of anti hypertensive agents examined.
In the primary placebo-controlled phase 3 clinical studies, data were analyzed for the incidence of adverse events in patients taking and not taking concomitant antihypertensive medications . There were no significant differences between the patient groups in the incidence of adverse events.

Medical Officers Comments:

A formal biopharm review was done by the particular division and the reviewer Dr Roy was consulted. IC351-Amoldipine interaction did show some additional hypotensive effect which was clinically insignificant in view of this reviewer.
However some interactions were done with IC 10mg IC 351. These may not be extrapolated to 20mg dose.

Pharmacodynamic Interactions with Organic Nitrates:

The potential for a pharmacodynamic interaction between 10 mg IC351 and organic nitrates was examined in 3 separate studies : LVAB, LVBY, and LVCM.
In these nitrate interaction studies, the greatest augmentation of the hypotensive effects of nitrates was typically seen within 4 hours of IC351 administration. However the effect lasted upto to 30 hours. In these studies the sponsors only used 10 mg dose of IC 351.

Medical Officers Comments:

The additive hypotensive effect of IC 351 on Nitrates is a major clinical concern in drugs of this class. A full evaluation of Nitrate – IC 351 interaction is needed along with the risk management plan.
The concomitant use of nitrate with IC 351 should be contraindicated.

9.5.6 .3 Cardiovascular Adverse Events

9.5.6.3.1 HYPOTENSION, SYNCOPE, AND VASODILATATION (FLUSHING)
According to the sponsor;

1. The clinical pharmacology studies showed that the incidence of postural hypotension and dizziness reported with IC351 treatment were not different from non-IC351 therapy.

2 . Of over 1000 subjects who received IC351 in clinical pharmacology studies, there were 7 subjects who had syncope after IC351 administration . Syncope was likely to have been vasovagal in 4 of these 7 subjects and was assessed as unrelated to study drug. Of these, three events occurred after venous cannulation, one event occurred during an eye examination, and one event occurred 2 days and 10 hours after dosing. In the remaining 3 subjects, the syncope occurred in subjects who took nitrates with IC351 during the comparative study LVCM with sildenafil of nitrate interactions. These episodes were due to postural hypotension following nitrate administration, although an augmentation of the blood pressure decrease by IC351 could not be ruled out. Two subjects who took nitrates and IC351 during the comparative study LVCM between IC351 and sildenafil also experienced syncope. Thus the cases of syncope that occurred in IC351-treated subjects were either vasovagal and not assessed as related

to study drug or seen in subjects who received organic nitrates concomitantly with IC351.

3)In the primary placebo-controlled phase 3 studies, there were no reports of hypotension or postural hypotension in IC351-treated patients compared with 1 occurrence of hypotension and 1 occurrence of postural hypotension in placebo-treated patients. There was one report of syncope in IC351-treated patients (event occurred in study LVDJ in patient 018-1851 who had a prior history of syncope, 2 days after the prior dose of IC351 and after 3 alcoholic drinks) and 2 reports of syncope in placebo-treated patients. None of these events were considered related to study drug. In all phase 2 and phase 3 studies, including the open-label studies, there were 2 reports of syncope in IC351-treated patients (studies LVDJ and LVBL) compared with 3 reports of syncope in placebo-treated patients (studies LVBJ and LVCQ) None of these events are assessed as related to study drug by the Sponsor.

In clinical pharmacology studies, the incidence of vasodilatation (flushing) was 5.6% in subjects who received IC351 and 4.8% in subjects who received placebo. In the primary placebo-controlled phase 3 studies, the incidence of flushing was 3.7 % for all IC351-treated patients compared to 1.6 % for placebo-treated patients.

Medical Officers Comments:

- The combination of Nitrates and IC351 has significant hypotensive effect. The incidence of dizziness and syncope was also higher in the Nitrate interaction studies.
- Vasodilation is an inherent mechanism of this drug. There should be a warning about the additive effects other vasodilator drugs (amoldipine , alcohol) when given with IC351.
- Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebro vascular hemorrhage, transient ischemic attack and hypertension, have been reported post-marketing in association with the use of another agent in this class. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity. So an extreme caution needs to be used in patients with risk of heart disease and these agents.

9.5.6.3. 2 ANGINA PECTORIS:

9 patients of angina pectoris were reported across IC 351 studies . 2 patients were in Patients in study LVBY, a drug-interaction study of IC351 with organic nitrates. All of them had a history and risk factor for this disease and investigators assessed the events to be unrelated to the drug.

Medical Officers Comments:

The data review did not causally link IC 351 to the occurence of angina pectoris in the studied population.

9.5.6.3.3 MYOCARDIAL INFARCTION AND CARDIAC MORTALITY:

Based upon the age and co-morbid conditions of the patients in the phase 2 and 3 trials, some cases of serious cardiovascular adverse events, including myocardial infarction, would be expected in the population of over 4000 patients studied.
Across all IC351 double-blind studies, there was one report of myocardial infarction inIC351-treated patients (study LVAC) and 3 reports of myocardial infarction in patients who did not take IC351: 2 in placebo-treated patients (study LVBK, LVCO) and 1 inpatient 117-9703 in study LVBK who was randomized to IC351, but who experienced a myocardial infarction prior to taking any study medication . In the two open-label long term safety studies, there were 9 reports of myocardial infarction, all of which occurred in study LVBL. Overall, there were 10 reports of myocardial infarction in patients taking IC351, or less than 0.65 per 100 patient-years, compared with 1.1 per 100 patient-years in patients who received placebo.
Overall, there were seven deaths reported in IC351 trials. Of these, four deaths were assessed as cardiac deaths. All the patients in this group had underlying cardiac condition and associated risk factors for the disease.

Medical Officers Comments:

1. The myocardial infarction rate in open label studies as well as the combined data on phase III studies shows comparability with placebo subjects and the rate in population at large.

2. The data submitted on MI's and cardiac mortality , is comparable with another drug in its class as well as general population. Upon review of the cases these serious events could not be directly attributed to the drug.

9.5.6.3.4 CONGESTIVE HEART FAILURE OR ARRHYTHMIA AND CEREBROVASCULAR EVENTS:

Cardiac events were reported in these categories. All were unrelated to IC 351 as assessed by the investigators.

Medical Officers Comments:

This reviewer could not unequivocally attribute these cardio vascular events to IC 351.

9.5.6.3.5 ELECTROCARDIOGRAMS

Electrocardiograms were obtained at screening and at final visit for the studies comprising this database except for LVCQ for which ECG will be obtained at the 6

month final visit. There were no significant differences in mean change from baseline to endpoint among the treatment groups for average heart rate, PR interval, QRS interval, QTc interval, and QT interval . There were no significant differences among treatment groups for a change from normal to abnormal ECGs over the course of the studies for the following parameters: axis abnormality, conduction disturbance, ischemia, morphology, myocardial infarction, supraventricular rhythm, ventricular rhythm, ST segment abnormality, or T wave abnormality . Under "other rhythm" parameters, there was a statistically significant difference among treatment groups, with the 2.5 mg IC351 group showing a higher rate of change of 29.1% from normal to abnormal compared with a lowest rate of change of 10.2% for the 20 mg IC351 group. The change for this "other rhythm" parameter for placebo was 17.4% and for all IC351-treated patients was 16.4%. This difference was not considered to be clinically significant.

Medical officer's comments:

- Clinically significant changes in electrocardiogram findings in IC351-treated patients vs placebo were not demonstrated .
- The data reviewed showed no unusual trends in QTc with the use of IC 351. However these studies tested 40mg as their highest dose.
- A cardio renal consult was done that essentially concluded that at a proposed 20mg marketing dose the safety margin (40mg max dose in Qt studies) was narrow for the QTc data submitted . From the submitted data there was no signal for QTc prolongation in the doses tested. However since the sponsor seeks only 20mg dose more studies are required to widen the safety margin.
- This makes a case for not approving 20mg at present .

9.5.6.4 Visual Adverse Events:

According to the sponsor , In clinical pharmacology and phase 2 and phase 3 studies of more than 4000 subjects who took IC351, no dose-related visual symptoms, especially of color tinge changes, occurred with multiple doses of 100 mg for 21 days (study LVBG) and single doses up to500 mg. There were three reports of abnormal color vision in the 4000 patients treated with IC351 (a rate <0.1%).

One healthy subject in the clinical pharmacology study LVCN (subject 48, 20 mg IC351)reported a single episode of chromatopsia (reported as blue vision) without anyabnormality in the Farnsworth-Munsell (FM) 100-hue test. Patient 212-6207 in the phase 3 study LVBN who had previously experienced a blue tinge to vision consistently after each dose while being treated with sildenafil, reported "visual field defect", described as visual color disturbance with red objects appearing blue and blue and yellow objects appearing orange following the 40th dose of 10 mg IC351; he took 13

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LIPITOR safely and effectively. See full prescribing information for LIPITOR.

LIPITOR® (atorvastatin calcium) tablets, for oral use
Initial U.S. Approval: 1996

----------RECENT MAJOR CHANGES----------

Contraindications, Pregnancy and Lactation (4)	Removed 12/2022
Warnings and Precautions, CNS Toxicity (5.5)	Removed 12/2022

----------INDICATIONS AND USAGE----------

LIPITOR is an HMG-CoA reductase inhibitor (statin) indicated (1):

- To reduce the risk of:
  - Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD.
  - MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD.
  - Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD.
- As an adjunct to diet to reduce low-density lipoprotein (LDL-C) in:
  - Adults with primary hyperlipidemia.
  - Adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other LDL-C-lowering therapies to reduce LDL-C in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia.
- As an adjunct to diet for the treatment of adults with:
  - Primary dysbetaliproteinemia.
  - Hypertriglyceridemia.

----------DOSAGE AND ADMINISTRATION----------

- Take orally once daily with or without food (2.1).
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating LIPITOR, and adjust dosage if necessary (2.1).
- *Adults* (2.2):
  - Recommended starting dosage is 10 or 20 mg once daily; dosage range is 10 mg to 80 mg once daily.
  - Patients requiring LDL-C reduction >45% may start at 40 mg once daily.
- *Pediatric Patients Aged 10 Years of Age and Older with HeFH*: Recommended starting dosage is 10 mg once daily; dosage range is 10 to 20 mg once daily (2.3).
- *Pediatric Patients Aged 10 Years of Age and Older with HoFH*: Recommended starting dosage is 10 to 20 mg once daily; dosage range is 10 to 80 mg once daily (2.4).
- See full prescribing information for LIPITOR dosage modifications due to drug interactions (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 10 mg; 20 mg; 40 mg; 80 mg of atorvastatin (3).

----------CONTRAINDICATIONS----------

- Acute liver failure or decompensated cirrhosis (4).
- Hypersensitivity to atorvastatin or any excipient in LIPITOR (4).

----------WARNINGS AND PRECAUTIONS----------

- *Myopathy and Rhabdomyolysis*: Risk factors include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher LIPITOR dosage. Discontinue LIPITOR if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Temporarily discontinue LIPITOR in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis. Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing LIPITOR dosage. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever (2.5, 5.1, 7.1, 8.5, 8.6).
- *Immune-Mediated Necrotizing Myopathy (IMNM)* Rare reports of IMNM, an autoimmune myopathy, have been reported with statin use. Discontinue LIPITOR if IMNM is suspected (5.2).
- *Hepatic Dysfunction* Increases in serum transaminases have occurred, some persistent. Rare reports of fatal and non-fatal hepatic failure have occurred. Consider testing liver enzymes before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIPITOR (5.3).

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥5%) are nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Viatris at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- See full prescribing information for details regarding concomitant use of LIPITOR with other drugs or grapefruit juice that increase the risk of myopathy and rhabdomyolysis (2.5, 7.1).
- *Rifampin*: May reduce atorvastatin plasma concentrations. Administer simultaneously with LIPITOR (7.2).
- *Oral Contraceptives* May increase plasma levels of norethindrone and ethinyl estradiol; consider this effect when selecting an oral contraceptive (7.3).
- *Digoxin* May increase digoxin plasma levels; monitor patients appropriately (7.3).

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy* May cause fetal harm. (8.1).
- *Lactation* Breastfeeding not recommended during treatment with LIPITOR (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LIPITOR is indicated:

- To reduce the risk of:
  - Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD
  - MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD
  - Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD
- As an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C) in:
  - Adults with primary hyperlipidemia.
  - Adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL-C in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).
- As an adjunct to diet for the treatment of adults with:
  - Primary dysbetalipoproteinemia
  - Hypertriglyceridemia

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

- Take Lipitor orally once daily at any time of the day, with or without food.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating LIPITOR, and adjust the dosage if necessary.

2.2 Recommended Dosage in Adult Patients

The recommended starting dosage of LIPITOR is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily. Patients who require reduction in LDL-C greater than 45% may be started at 40 mg once daily.

2.3 Recommended Dosage in Pediatric Patients 10 Years of Age and Older with HeFH

The recommended starting dosage of LIPITOR is 10 mg once daily. The dosage range is 10 mg to 20 mg once daily.

2.4 Recommended Dosage in Pediatric Patients 10 Years of Age and Older with HoFH

The recommended starting dosage of LIPITOR is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily.

2.5 Dosage Modifications Due to Drug Interactions

Concomitant use of LIPITOR with the following drugs requires dosage modification of LIPITOR *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

Anti-Viral Medications

- In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed LIPITOR 20 mg once daily.
- In patients taking nelfinavir, do not exceed LIPITOR 40 mg once daily.

Select Azole Antifungals or Macrolide Antibiotics

- In patients taking clarithromycin or itraconazole, do not exceed LIPITOR 20 mg once daily.

For additional recommendations regarding concomitant use of LIPITOR with other anti-viral medications, azole antifungals or macrolide antibiotics, *see Drug Interactions (7.1).*

3 DOSAGE FORMS AND STRENGTHS

LIPITOR tablets:

- 10 mg of atorvastatin: white elliptical, film-coated tablets with “PD 155” on one side and “10” on the other
- 20 mg of atorvastatin: white elliptical, film-coated tablets with “PD 156” on one side and “20” on the other
- 40 mg of atorvastatin: white elliptical, film-coated tablets with “PD 157” on one side and “40” on the other
- 80 mg of atorvastatin: white elliptical, film-coated tablets with “PD 158” on one side and “80” on the other

4 CONTRAINDICATIONS

- Acute liver failure or decompensated cirrhosis *[see Warnings and Precautions (5.3)]*
- Hypersensitivity to atorvastatin or any excipients in LIPITOR. Hypersensitivity reactions, including anaphylaxis, angioneurotic edema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

LIPITOR may cause myopathy (muscle pain, tenderness, or weakness associated with elevated creatine kinase [CK]) and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis in patients treated with statins, including LIPITOR.

Risk Factors for Myopathy
Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs (including other lipid-lowering therapies), and higher LIPITOR dosage *[see Drug Interactions (7.1) and Use in Specific Populations (8.5, 8.6)]*.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis
LIPITOR exposure may be increased by drug interactions due to inhibition of cytochrome P450 enzyme 3A4 (CYP3A4) and/or transporters (e.g., breast cancer resistant protein [BCRP], organic anion-transporting polypeptide [OATP1B1/OATP1B3] and P-glycoprotein [P-gp]), resulting in an increased risk of myopathy and rhabdomyolysis. Concomitant use of cyclosporine, gemfibrozil, tipranavir plus ritonavir, or glecaprevir plus pibrentasvir with LIPITOR is not recommended. LIPITOR dosage modifications are recommended for patients taking certain anti-viral, azole antifungals, or macrolide antibiotic medications *[see Dosage and Administration (2.5)]*. Cases of myopathy/rhabdomyolysis have been reported with atorvastatin co-administered with lipid modifying doses (>1 gram/day) of niacin, fibrates, colchicine, and ledipasvir plus sofosbuvir. Consider if the benefit of use of these products outweighs the increased risk of myopathy and rhabdomyolysis *[see Drug Interactions (7.1)]*.

Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking LIPITOR *[see Drug Interactions (7.1)]*.

Discontinue LIPITOR if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if LIPITOR is discontinued. Temporarily discontinue LIPITOR in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the LIPITOR dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

5.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or a different statin was administered. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase that persists despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue LIPITOR if IMNM is suspected.

5.3 Hepatic Dysfunction

Increases in serum transaminases have been reported with use of LIPITOR *[see Adverse Reactions (6.1)]*. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. Persistent increases to more than three times the ULN in serum transaminases have occurred in approximately 0.7% of patients receiving LIPITOR in clinical trials. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including LIPITOR.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury *[see Use in Specific Populations (8.7)]*.

Consider liver enzyme testing before LIPITOR initiation and when clinically indicated thereafter. LIPITOR is contraindicated in patients with acute liver failure or decompensated cirrhosis *[see Contraindications (4)]*. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIPITOR.

5.4 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including LIPITOR. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

5.5 Increased Risk of Hemorrhagic Stroke in Patients on LIPITOR 80 mg with Recent Hemorrhagic Stroke

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial where 2365 adult patients, without CHD who had a stroke or TIA within the preceding 6 months, were treated with LIPITOR 80 mg, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to placebo (55, 2.3% LIPITOR vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of non-fatal hemorrhagic stroke was significantly higher in the LIPITOR group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the LIPITOR group *[see Adverse Reactions (6.1)]*. Consider the risk/benefit of use of LIPITOR 80 mg in patients with recent hemorrhagic stroke.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Myopathy and Rhabdomyolysis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Necrotizing Myopathy *[see Warnings and Precautions (5.2)]*
- Hepatic Dysfunction *[see Warnings and Precautions (5.3)]*
- Increases in HbA1c and Fasting Serum Glucose Levels *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the LIPITOR placebo-controlled clinical trial database of 16,066 patients (8755 LIPITOR vs. 7311 placebo; age range 10-93 years, 39% women, 91% White, 3% Black, 2% Asian, 4% other) with a median treatment duration of 53 weeks, the most common adverse reactions in patients treated with LIPITOR that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

Table 1 summarizes adverse reactions reported in ≥ 2% and at a rate greater than placebo in patients treated with LIPITOR (n=8755), from seventeen placebo-controlled trials.

Table 1: Adverse Reactions Occurring in ≥ 2% in Patients LIPITOR-Treated with any Dose and Greater than Placebo

Adverse Reaction	% Placebo N=7311	% 10 mg N=3908	% 20 mg N=188	% 40 mg N=604	% 80 mg N=4055	% Any dose N=8755
Nasopharyngitis	8.2	12.9	5.3	7.0	4.2	8.3
Arthralgia	6.5	8.9	11.7	10.6	4.3	6.9
Diarrhea	6.3	7.3	6.4	14.1	5.2	6.8
Pain in extremity	5.9	8.5	3.7	9.3	3.1	6.0
Urinary tract infection	5.6	6.9	6.4	8.0	4.1	5.7
Dyspepsia	4.3	5.9	3.2	6.0	3.3	4.7
Nausea	3.5	3.7	3.7	7.1	3.8	4.0
Musculoskeletal pain	3.6	5.2	3.2	5.1	2.3	3.8
Muscle spasms	3.0	4.6	4.8	5.1	2.4	3.6
Myalgia	3.1	3.6	5.9	8.4	2.7	3.5
Insomnia	2.9	2.8	1.1	5.3	2.8	3.0

Pharyngolaryngeal pain	2.1	3.9	1.6	2.8	0.7	2.3

Other adverse reactions reported in placebo-controlled trials include:
Body as a whole: malaise, pyrexia
Digestive system: abdominal discomfort, eructation, flatulence, hepatitis, cholestasis
Musculoskeletal system: musculoskeletal pain, muscle fatigue, neck pain, joint swelling
Metabolic and nutritional system: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia
Nervous system: nightmare
Respiratory system: epistaxis
Skin and appendages: urticaria
Special senses: vision blurred, tinnitus
Urogenital system: white blood cells urine positive

Elevations in Liver Enzyme Tests
Persistent elevations in serum transaminases, defined as more than 3 times the ULN and occurring on 2 or more occasions, occurred in 0.7% of patients who received LIPITOR in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver enzyme tests in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent liver enzyme elevations continued treatment with a reduced dose of LIPITOR.

Treating to New Targets Study (TNT)
In TNT, *[see Clinical Studies (14.1)]* 10,001 patients (age range 29-78 years, 19% women; 94% White, 3% Black, 1% Asian, 2% other) with clinically evident CHD were treated with LIPITOR 10 mg daily (n=5006) or LIPITOR 80 mg daily (n=4995). In the high-dose LIPITOR group, there were more patients with serious adverse reactions (1.8%) and discontinuations due to adverse reactions (9.9%) as compared to the low-dose group (1.4%; 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4-10 days) occurred in 1.3% of individuals with LIPITOR 80 mg and in 0.2% of individuals with LIPITOR 10 mg. Elevations of CK (≥ 10 x ULN) were higher in the high-dose LIPITOR group (0.3%) compared to the low-dose LIPITOR group (0.1%).

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In SPARCL, 4731 patients (age range 21-92 years, 40% women; 93% White, 3% Black, 1% Asian, 3% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months were treated with LIPITOR 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years. There was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice within 4-10 days) in the LIPITOR group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x ULN) were rare, but were higher in the LIPITOR group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 6.1% of subjects in the LIPITOR group and 3.8% of subjects in the placebo group.

In a post-hoc analysis, LIPITOR 80 mg reduced the incidence of ischemic stroke (9.2% vs. 11.6%) and increased the incidence of hemorrhagic stroke (2.3% vs. 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 LIPITOR vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the LIPITOR group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Patients who entered the trial with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke (16% LIPITOR vs. 4% placebo).

Adverse Reactions from Clinical Studies of LIPITOR in Pediatric Patients with HeFH
In a 26-week controlled study in pediatric patients with HeFH (ages 10 years to 17 years) (n=140, 31% female; 92% White, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of LIPITOR 10 to 20 mg daily, as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels, was generally similar to that of placebo *[see Use in Specific Populations (8.4) and Clinical Studies (14.6)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LIPITOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: pancreatitis
General disorders: fatigue

Hepatobiliary Disorders: fatal and non-fatal hepatic failure
Immune system disorders: anaphylaxis
Injury: tendon rupture
Musculoskeletal and connective tissue disorders: rhabdomyolysis, myositis.
There have been rare reports of immune-mediated necrotizing myopathy associated with statin use.
Nervous system disorders: dizziness, peripheral neuropathy.
There have been rare reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with the use of all statins. Cognitive impairment was generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).
Psychiatric disorders: depression
Respiratory disorders: interstitial lung disease
Skin and subcutaneous tissue disorders: angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis)

7 DRUG INTERACTIONS

7.1 Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with LIPITOR

LIPITOR is a substrate of CYP3A4 and transporters (e.g., OATP1B1/1B3, P-gp, or BCRP). LIPITOR plasma levels can be significantly increased with concomitant administration of inhibitors of CYP3A4 and transporters. Table 2 includes a list of drugs that may increase exposure to LIPITOR and may increase the risk of myopathy and rhabdomyolysis when used concomitantly and instructions for preventing or managing them *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Table 2: Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with LIPITOR

Cyclosporine or Gemfibrozil	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of LIPITOR and cyclosporine, an inhibitor of CYP3A4 and OATP1B1 *[see Clinical Pharmacology (12.3)]*. Gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with LIPITOR.
Intervention:	Concomitant use of cyclosporine or gemfibrozil with LIPITOR is not recommended.
Anti-Viral Medications	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of LIPITOR with many anti-viral medications, which are inhibitors of CYP3A4 and/or transporters (e.g., BCRP, OATP1B1/1B3, P-gp, MRP2, and/or OAT2) *[see Clinical Pharmacology (12.3)]*. Cases of myopathy and rhabdomyolysis have been reported with concomitant use of ledipasvir plus sofosbuvir with LIPITOR.
Intervention:	• Concomitant use of tipranavir plus ritonavir or glecaprevir plus pibrentasvir with LIPITOR is not recommended. • In patients taking lopinavir plus ritonavir, or simeprevir, consider the risk/benefit of concomitant use with atorvastatin. • In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed LIPITOR 20 mg. • In patients taking nelfinavir, do not exceed LIPITOR 40 mg *[see Dosage and Administration (2.5)]*. • Consider the risk/benefit of concomitant use of ledipasvir plus sofosbuvir with LIPITOR. • Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Tipranavir plus ritonavir, glecaprevir plus pibrentasvir, lopinavir plus ritonavir, simeprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir, letermovir, nelfinavir, and ledipasvir plus sofosbuvir.
Select Azole Antifungals or Macrolide Antibiotics	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of LIPITOR with select azole antifungals or macrolide antibiotics, due to inhibition of CYP3A4 and/or transporters *[see Clinical Pharmacology (12.3)]*.
Intervention:	In patients taking clarithromycin or itraconazole, do not exceed LIPITOR 20 mg *[see Dosage and Administration (2.5)]*. Consider the risk/benefit of concomitant use of other azole antifungals or

	macrolide antibiotics with LIPITOR. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole.
Niacin	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been observed with concomitant use of lipid modifying dosages of niacin (≥1 gram/day niacin) with LIPITOR.
Intervention:	Consider if the benefit of using lipid modifying dosages of niacin concomitantly with LIPITOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Fibrates (other than Gemfibrozil)	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with LIPITOR.
Intervention:	Consider if the benefit of using fibrates concomitantly with LIPITOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Colchicine	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with LIPITOR.
Intervention:	Consider the risk/benefit of concomitant use of colchicine with LIPITOR. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Grapefruit Juice	
Clinical Impact:	Grapefruit juice consumption, especially excessive consumption, more than 1.2 liters/daily, can raise the plasma levels of atorvastatin and may increase the risk of myopathy and rhabdomyolysis.
Intervention:	Avoid intake of large quantities of grapefruit juice, more than 1.2 liters daily, when taking LIPITOR.

7.2 Drug Interactions that may Decrease Exposure to LIPITOR

Table 3 presents drug interactions that may decrease exposure to LIPITOR and instructions for preventing or managing them.

Table 3: Drug Interactions that may Decrease Exposure to LIPITOR

Rifampin	
Clinical Impact:	Concomitant administration of LIPITOR with rifampin, an inducer of cytochrome P450 3A4 and inhibitor of OATP1B1, can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, delayed administration of LIPITOR after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.
Intervention:	Administer LIPITOR and rifampin simultaneously.

7.3 LIPITOR Effects on Other Drugs

Table 4 presents LIPITOR's effect on other drugs and instructions for preventing or managing them.

Table 4: LIPITOR Effects on Other Drugs

Oral Contraceptives	
Clinical Impact:	Co-administration of LIPITOR and an oral contraceptive increased plasma concentrations of norethindrone and ethinyl estradiol *[see Clinical Pharmacology (12.3)]*.
Intervention:	Consider this when selecting an oral contraceptive for patients taking LIPITOR.
Digoxin	
Clinical Impact:	When multiple doses of LIPITOR and digoxin were co-administered, steady state plasma digoxin concentrations increased *[see Clinical Pharmacology (12.3)]*.
Intervention:	Monitor patients taking digoxin appropriately.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Discontinue LIPITOR when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. LIPITOR decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol; therefore, LIPITOR may cause fetal harm when administered to pregnant patients based on the mechanism of action *[see Clinical Pharmacology (12.1)]*. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

Available data from case series and prospective and retrospective observational cohort studies over decades of use with statins in pregnant women have not identified a drug-associated risk of major congenital malformations. Published data from prospective and retrospective observational cohort studies with LIPITOR use in pregnant women are insufficient to determine if there is a drug-associated risk of miscarriage *(see Data)*. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats or rabbits orally administered atorvastatin at doses that resulted in up to 30 and 20 times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 80 mg, based on body surface area (mg/m^2). In rats administered atorvastatin during gestation and lactation, decreased postnatal growth and development delay were observed at doses ≥ 6 times the MRHD *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

A Medicaid cohort linkage study of 1152 statin-exposed pregnant women compared to 886,996 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders – including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use – using propensity score-based methods. The relative risk of congenital malformations between the group with statin use and the group with no statin use in the first trimester was 1.07 (95% confidence interval 0.85 to 1.37) after controlling for confounders, particularly pre-existing diabetes mellitus. There were also no statistically significant increases in any of the organ-specific malformations assessed after accounting for confounders. In the majority of pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence of a malformation, lack of control for certain confounders such as body mass index, use of prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

Animal Data

Atorvastatin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure at the MRHD based on surface area (mg/m^2). In rats, the maternally toxic dose of 300 mg/kg resulted in increased post-implantation loss and decreased fetal body weight. At the maternally toxic doses of 50 and 100 mg/kg/day in rabbits, there was increased post-implantation loss, and at 100 mg/kg/day fetal body weights were decreased.

In a study in pregnant rats administered 20, 100, or 225 mg/kg/day from gestation day 7 through to lactation day 20 (weaning), there was decreased survival at birth, postnatal day 4, weaning, and post-weaning in pups of mothers dosed with 225 mg/kg/day, a dose at which maternal toxicity was observed. Pup body weight was decreased through postnatal day 21 at 100 mg/kg/day, and through postnatal day 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human exposure at the MRHD, based on AUC.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma.

8.2 Lactation

Risk Summary

There is no information about the presence of atorvastatin in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. However, it has been shown that another drug in this class passes into human milk. Studies in rats have shown that atorvastatin and/or its metabolites are present in the breast milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk *(see Data)*. Statins, including LIPITOR, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant.

Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action, advise patients that breastfeeding is not recommended during treatment with LIPITOR *[see Use in Specific Populations (8.1), Clinical Pharmacology (12.1)]*.

Data
Following a single oral administration of 10 mg/kg of radioactive atorvastatin to lactating rats, the concentration of total radioactivity was determined. Atorvastatin and/or its metabolites were measured in the breast milk and pup plasma at a 2:1 ratio (milk:plasma).

8.4 Pediatric Use

The safety and effectiveness of LIPITOR as an adjunct to diet to reduce LDL-C have been established pediatric patients 10 years of age and older with HeFH. Use of LIPITOR for this indication is based on a double-blind, placebo-controlled clinical trial in 187 pediatric patients 10 years of age and older with HeFH. In this limited controlled trial, there was no significant effect on growth or sexual maturation in the boys or girls, or on menstrual cycle length in girls.

The safety and effectiveness of LIPITOR as an adjunct to other LDL-C-lowering therapies to reduce LDL-C have been established pediatric patients 10 years of age and older with HoFH. Use of LIPITOR for this indication is based on a trial without a concurrent control group in 8 pediatric patients 10 years of age and older with HoFH *[see Clinical Studies (14)]*.

The safety and effectiveness of LIPITOR have not been established in pediatric patients younger than 10 years of age with HeFH or HoFH, or in pediatric patients with other types of hyperlipidemia (other than HeFH or HoFH).

8.5 Geriatric Use

Of the total number of LIPITOR-treated patients in clinical trials, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Advanced age (≥65 years) is a risk factor for LIPITOR-associated myopathy and rhabdomyolysis. Dose selection for an elderly patient should be cautious, recognizing the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of myopathy. Monitor geriatric patients receiving LIPITOR for the increased risk of myopathy *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor all patients with renal impairment for development of myopathy. Renal impairment does not affect the plasma concentrations of LIPITOR, therefore there is no dosage adjustment in patients with renal impairment *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

In patients with chronic alcoholic liver disease, plasma concentrations of LIPITOR are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease. LIPITOR is contraindicated in patients with acute liver failure or decompensated cirrhosis *[see Contraindications (4)]*.

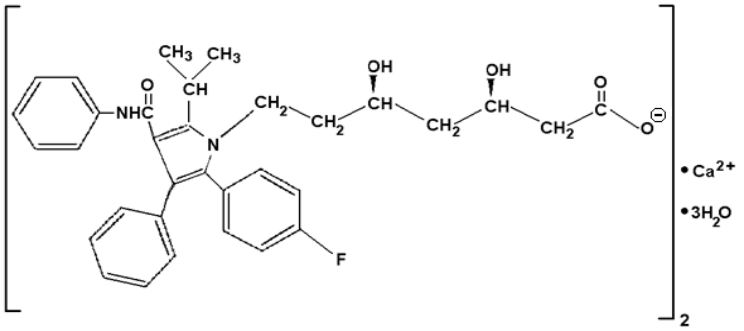
10 OVERDOSAGE

No specific antidotes for LIPITOR are known. Contact Poison Control (1-800-222-1222) for latest recommendations. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance LIPITOR clearance.

11 DESCRIPTION

LIPITOR (atorvastatin) is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

LIPITOR tablets for oral use contain atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg (equivalent to 10.36 mg, 20.72 mg, 41.44 mg, or 82.88 mg atorvastatin calcium anhydrous) and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LIPITOR is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. In animal models, LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; LIPITOR also reduces LDL production and the number of LDL particles.

12.2 Pharmacodynamics

LIPITOR, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response *[see Dosage and Administration (2)]*.

12.3 Pharmacokinetics

Absorption
LIPITOR is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to LIPITOR dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether LIPITOR is given with or without food. Plasma LIPITOR concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution
Mean volume of distribution of LIPITOR is approximately 381 liters. LIPITOR is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Elimination
Metabolism
LIPITOR is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of LIPITOR. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of LIPITOR metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of LIPITOR in humans following

co-administration with erythromycin, a known inhibitor of this isozyme *[see Drug Interactions (7.1)]*. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion
LIPITOR and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of LIPITOR in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of LIPITOR is recovered in urine following oral administration.

Specific Populations

Geriatric
Plasma concentrations of LIPITOR are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults.

Pediatric
Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in atorvastatin population PK model with data including pediatric HeFH patients (ages 10 years to 17 years of age, n=29) in an open-label, 8-week study.

Gender
Plasma concentrations of LIPITOR in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with LIPITOR between men and women.

Renal Impairment
Renal disease has no influence on the plasma concentrations or LDL-C reduction of LIPITOR *[see Use in Specific Populations (8.6)]*.

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of LIPITOR since the drug is extensively bound to plasma proteins.

Hepatic Impairment
In patients with chronic alcoholic liver disease, plasma concentrations of LIPITOR are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease *[see Use in Specific Populations (8.7)]*.

Drug Interactions

Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporter BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Table 5: Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	**Atorvastatin**		
	Dose (mg)	**Ratio of AUC[&]**	**Ratio of Cmax[&]**
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD[a] for 28 days	8.69	10.66
[#]Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days	10 mg SD[c]	9.36	8.58
[#]Glecaprevir 400 mg QD[a]/pibrentasvir 120 mg QD[a], 7 days	10 mg QD[a] for 7 days	8.28	22.00
[#]Telaprevir 750 mg q8h[f], 10 days	20 mg SD[c]	7.88	10.60
[#,‡]Saquinavir 400 mg BID[b]/ritonavir 400 mg BID[b], 15 days	40 mg QD[a] for 4 days	3.93	4.31
[#]Elbasvir 50 mg QD[a]/grazoprevir 200 mg QD[a], 13 days	10 mg SD[c]	1.94	4.34
[#]Simeprevir 150 mg QD[a], 10 days	40 mg SD[c]	2.12	1.70
[#]Clarithromycin 500 mg BID[b], 9 days	80 mg QD[a] for 8 days	4.54	5.38
[#]Darunavir 300 mg BID[b]/ritonavir 100 mg BID[b], 9 days	10 mg QD[a] for 4 days	3.45	2.25

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	**Ratio of AUC[&]**	**Ratio of Cmax[&]**
[#]Itraconazole 200 mg QD[a], 4 days	40 mg SD[c]	3.32	1.20
[#]Letermovir 480 mg QD[a], 10 days	20 mg SD[c]	3.29	2.17
[#]Fosamprenavir 700 mg BID[b]/ritonavir 100 mg BID[b], 14 days	10 mg QD[a] for 4 days	2.53	2.84
[#]Fosamprenavir 1400 mg BID[b], 14 days	10 mg QD[a] for 4 days	2.30	4.04
[#]Nelfinavir 1250 mg BID[b], 14 days	10 mg QD[a] for 28 days	1.74	2.22
[#]Grapefruit Juice, 240 mL QD[a,*]	40 mg SD[c]	1.37	1.16
Diltiazem 240 mg QD[a], 28 days	40 mg SD[c]	1.51	1.00
Erythromycin 500 mg QID[e], 7 days	10 mg SD[c]	1.33	1.38
Amlodipine 10 mg, single dose	80 mg SD[c]	1.18	0.91
Cimetidine 300 mg QID[e], 2 weeks	10 mg QD[a] for 2 weeks	1.00	0.89
Colestipol 10 g BID[b], 24 weeks	40 mg QD[a] for 8 weeks	NA	0.74**
Maalox TC® 30 mL QID[e], 17 days	10 mg QD[a] for 15 days	0.66	0.67
Efavirenz 600 mg QD[a], 14 days	10 mg for 3 days	0.59	1.01
[#]Rifampin 600 mg QD[a], 7 days (co-administered) [†]	40 mg SD[c]	1.12	2.90
[#]Rifampin 600 mg QD[a], 5 days (doses separated)[†]	40 mg SD[c]	0.20	0.60
[#]Gemfibrozil 600 mg BID[b], 7 days	40 mg SD[c]	1.35	1.00
[#]Fenofibrate 160 mg QD[a], 7 days	40 mg SD[c]	1.03	1.02
Boceprevir 800 mg TID[d], 7 days	40 mg SD[c]	2.32	2.66

[&] Represents ratio of treatments (co-administered drug plus atorvastatin vs. atorvastatin alone).

[#] See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (ratio of AUC up to 2.5) and/or Cmax (ratio of Cmax up to 1.71) have been reported with excessive grapefruit consumption (≥ 750 mL-1.2 liters per day).

** Ratio based on a single sample taken 8-16 h post dose.

[†] Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

[‡] The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

[a] Once daily

[b] Twice daily

[c] Single dose

[d] Three times daily

[e] Four times daily

[f] Every 8 hours

Table 6: Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	**Ratio of AUC**	**Ratio of Cmax**
80 mg QD[a] for 15 days	Antipyrine, 600 mg SD[c]	1.03	0.89
80 mg QD[a] for 10 days	[#] Digoxin 0.25 mg QD[a], 20 days	1.15	1.20
40 mg QD[a] for 22 days	Oral contraceptive QD[a], 2 months - norethindrone 1 mg - ethinyl estradiol 35 µg	 1.28 1.19	 1.23 1.30
10 mg SD[c]	Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days	1.08	0.96
10 mg QD[a] for 4 days	Fosamprenavir 1400 mg BID[b], 14 days	0.73	0.82
10 mg QD[a] for 4 days	Fosamprenavir 700 mg BID[b]/ritonavir 100 mg BID[b], 14 days	0.99	0.94

[#] See Section 7 for clinical significance.

[a] Once daily
[b] Twice daily
[c] Single dose

LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

In female rats, atorvastatin at doses up to 225 mg/kg (56 times the human exposure) did not cause adverse effects on fertility. Studies in male rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for 2 years.

14 CLINICAL STUDIES

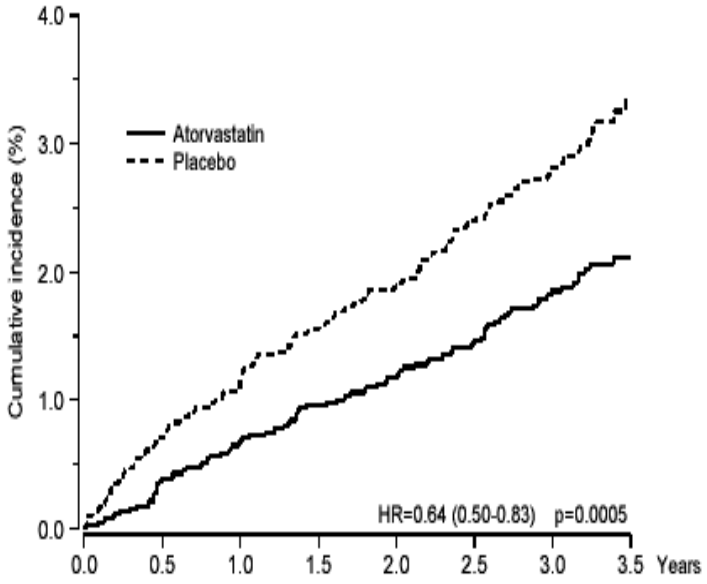
Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR on fatal and non-fatal coronary heart disease was assessed in 10,305 patients with hypertension, 40-80 years of age (mean of 63 years; 19% women; 95% White, 3% Black, 1% South Asian, 1% other), without a previous myocardial infarction and with total cholesterol (TC) levels ≤251 mg/dL. Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81%), age >55 years (85%), smoking (33%), diabetes (24%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14%), peripheral vascular disease (5%), left ventricular hypertrophy (14%), prior cerebrovascular event (10%), specific ECG abnormality (14%), proteinuria/albuminuria (62%). In this double-blind, placebo-controlled trial, patients were treated with anti-hypertensive therapy (goal BP <140/90 mm Hg for patients without diabetes; <130/80 mm Hg for patients with diabetes) and allocated to either LIPITOR 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of LIPITOR on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the LIPITOR group) or non-fatal MI (108 events in the placebo group vs. 60 events in the LIPITOR group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for LIPITOR vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels.

Figure 1: Effect of LIPITOR 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



LIPITOR also significantly decreased the relative risk for revascularization procedures by 42% (incidences of 1.4% for LIPITOR and 2.5% for placebo). Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for LIPITOR and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of LIPITOR on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% White, 2% Black, 2% South Asian, 1% other; 68% male), ages 40-75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤160 mg/dL and triglycerides (TG) ≤600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the trial. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either LIPITOR 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA1c 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

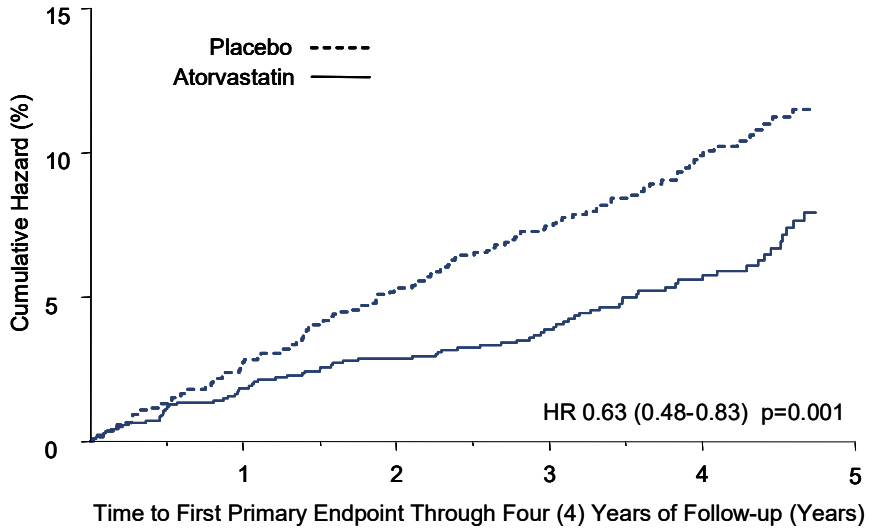
The effect of LIPITOR 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the LIPITOR group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 2). An effect of LIPITOR was seen regardless of age, sex, or baseline lipid levels.

LIPITOR significantly reduced the risk of stroke by 48% (21 events in the LIPITOR group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the LIPITOR group vs. 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the LIPITOR group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

Figure 2: Effect of LIPITOR 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



In the Treating to New Targets Study (TNT), the effect of LIPITOR 80 mg/day vs. LIPITOR 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% White, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with LIPITOR 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of LIPITOR and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of LIPITOR and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of LIPITOR.

Treatment with LIPITOR 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p=0.0002 (see Figure 3 and Table 7). The overall risk reduction was consistent regardless of age (<65, ≥65) or sex.

Figure 3: Effect of LIPITOR 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

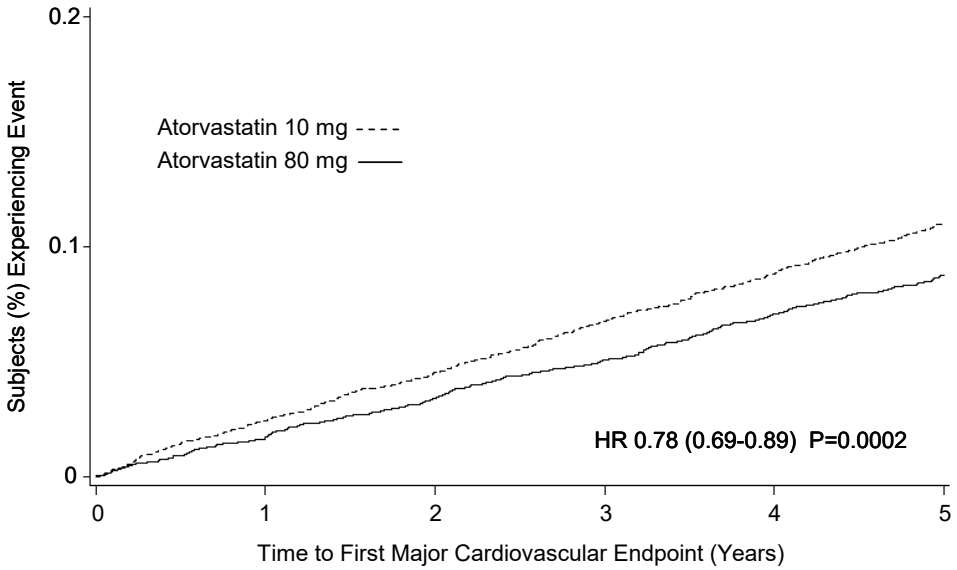


Table 7: Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	

First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

[a] Atorvastatin 80 mg: atorvastatin 10 mg
[b] Component of other secondary endpoints
* Secondary endpoints not included in primary endpoint
HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft
Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of the events that comprised the primary efficacy endpoint, treatment with LIPITOR 80 mg/day significantly reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 7). Of the predefined secondary endpoints, treatment with LIPITOR 80 mg/day significantly reduced the rate of coronary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 7). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the LIPITOR 80 mg group than in the LIPITOR 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the LIPITOR 80 mg group than in the LIPITOR 10 mg treatment group.

Primary Hyperlipidemia in Adults

LIPITOR reduces total-C, LDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

In two multicenter, placebo-controlled, dose-response trials in patients with hyperlipidemia, LIPITOR given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 8.)

Table 8: Dose Response in Patients with Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C
Placebo	21	4	4	3	10	-3
10	22	-29	-39	-32	-19	6
20	20	-33	-43	-35	-26	9
40	21	-37	-50	-42	-29	6
80	23	-45	-60	-50	-37	5

[a] Results are pooled from 2 dose-response trials.

In three multicenter, double-blind trials in patients with hyperlipidemia, LIPITOR was compared to other statins. After randomization, patients were treated for 16 weeks with either LIPITOR 10 mg per day or a fixed dose of the comparative agent (Table 9).

Table 9: Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C
Trial 1						
LIPITOR 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7
Lovastatin 20 mg	191	-19	-27	-20	-6	+7
95% CI for Diff[l]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0
Trial 2						
LIPITOR 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6
Pravastatin 20 mg	77	-17	-23	-17	-9	+8
95% CI for Diff[l]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6
Trial 3						
LIPITOR 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7
Simvastatin 10 mg	45	-24	-30	-30	-15	+7
95% CI for Diff[l]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9

[1] A negative value for the 95% CI for the difference between treatments favors LIPITOR for all except HDL-C, for which a positive value favors LIPITOR. If the range does not include 0, this indicates a statistically significant difference.
[a] Significantly different from lovastatin, ANCOVA, $p \leq 0.05$
[b] Significantly different from pravastatin, ANCOVA, $p \leq 0.05$
[c] Significantly different from simvastatin, ANCOVA, $p \leq 0.05$

Table 9 does not contain data comparing the effects of LIPITOR 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the trials summarized in the table are not necessarily interchangeable.

Hypertriglyceridemia in Adults

The response to LIPITOR in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 10). For the LIPITOR-treated patients, median (min, max) baseline TG level was 565 (267-1502).

Table 10: Combined Patients with Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

	Placebo (N=12)	LIPITOR 10 mg (N=37)	LIPITOR 20 mg (N=13)	LIPITOR 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

Dysbetalipoproteinemia in Adults

The results of an open-label crossover trial of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia are shown in the table below (Table 11).

Table 11: Open-Label Crossover Trial of 16 Patients with Dysbetalipoproteinemia (*Fredrickson* Type III)

		Median % Change (min, max)	
	Median (min, max) at Baseline (mg/dL)	LIPITOR 10 mg	LIPITOR 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

HoFH in Adults and Pediatric Patients

In a trial without a concurrent control group, 29 patients (mean age of 22 years, median age of 24 years, 31% <18 years) with HoFH received maximum daily doses of 20 to 80 mg of LIPITOR. The mean LDL-C reduction in this trial was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

HeFH in Pediatric Patients

In a double-blind, placebo-controlled trial followed by an open-label phase, 187 boys and post-menarchal girls 10 years to 17 years of age (mean age 14.1 years; 31% female; 92% White, 1.6% Blacks, 1.6% Asians, 4.8% other) with heterozygous familial hypercholesterolemia (HeFH) or severe hypercholesterolemia, were randomized to LIPITOR (n=140) or placebo (n=47) for 26 weeks and then all received LIPITOR for 26 weeks. Inclusion in the trial required 1) a baseline LDL-C level ≥190 mg/dL or 2) a baseline LDL-C level ≥160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 219 mg/dL (range: 139-385 mg/dL) in the LIPITOR group compared to 230 mg/dL (range: 160-325 mg/dL) in the placebo group. The dosage of LIPITOR (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was >130 mg/dL. The number of LIPITOR-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 78 (56%).

LIPITOR significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 12).

Table 12: Lipid-altering Effects of LIPITOR in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
LIPITOR	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the LIPITOR group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

Atorvastatin was also studied in a three year open-label, uncontrolled trial that included 163 patients with HeFH who were 10 years to 15 years old (82 boys and 81 girls). All patients had a clinical diagnosis of HeFH confirmed by genetic analysis (if not already confirmed by family history). Approximately 98% were White, and less than 1% were Black or Asian. Mean LDL-C at baseline was 232 mg/dL. The starting atorvastatin dosage was 10 mg once daily and doses were adjusted to achieve a target of <130 mg/dL LDL-C. The reductions in LDL-C from baseline were generally consistent across age groups within the trial as well as with previous clinical trials in both adult and pediatric placebo-controlled trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

LIPITOR tablets are supplied as follows:

Strength	How Supplied	NDC	Tablet Description

10 mg of atorvastatin	bottles of 90	0071-0155-23	white elliptical, film-coated tablets with "PD 155" on one side and "10" on the other
	10 x 10 unit dose blisters	0071-0155-40	
20 mg of atorvastatin	bottles of 90	0071-0156-23	white elliptical, film-coated tablets with "PD 156" on one side and "20" on the other
	10 x 10 unit dose blisters	0071-0156-40	
40 mg of atorvastatin	bottles of 90	0071-0157-23	white elliptical, film-coated tablets with "PD 157" on one side and "40" on the other
	10 x 10 unit dose blisters	0071-0157-40	
80 mg of atorvastatin	bottles of 90	0071-0158-23	white elliptical, film-coated tablets with "PD 158" on one side and "80" on the other
	8 x 8 unit dose blisters	0071-0158-92	

Storage
Store at controlled room temperature 20 - 25°C (68 - 77°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myopathy and Rhabdomyolysis
Advise patients that LIPITOR may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication or consuming large quantities of grapefruit juice and they should discuss all medication, both prescription and over the counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever *[see Warnings and Precautions (5.1), Drug Interactions (7.1)]*.

Hepatic Dysfunction
Inform patients that LIPITOR may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice *[see Warnings and Precautions (5.3)]*.

Increases in HbA1c and Fasting Serum Glucose Levels
Inform patients that increases in HbA1c and fasting serum glucose levels may occur with LIPITOR. Encourage patients to optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices *[see Warnings and Precautions (5.4)]*.

Pregnancy
Advise pregnant patients and patients who can become pregnant of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if LIPITOR should be discontinued *[see Use in Specific Populations (8.1)]*.

Lactation
Advise patients that breastfeeding is not recommended during treatment with LIPITOR *[see Use in Specific Populations (8.2)]*.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.lipitor.com.

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CPK elevations

Introduction

Myalgia is a relatively common symptom among patients treated with HMGRIs and was reported by 34/2502 (1.4%) of atorvastatin treated patients studied here. Musculoskeletal complaints were offered by over 20% of both atorvastatin and combined HMGRIs patients. Frank myopathy, which occurs very rarely with this class of drugs, is signaled by the occurrence of muscle pain or tenderness in association with elevated CPK and may lead to rhabdomyolysis, especially in patients with renal insufficiency. The muscle effects of the HMGRIs are presumed to be related to the mechanism of action of the drug, but because of their infrequent occurrence, must be considered idiosyncratic. The risk of myositis, myopathy, and rhabdomyolysis are known to be increased by concomitant use of HMGRIs and certain other agents, including the fibrates, cyclosporine, erythromycin, and itraconazole. The mechanism of this enhanced toxicity is felt due to increase in systemic levels of HMGRI because of inhibition of hepatic drug metabolizing enzymes, specifically cytochrome P450 CYP3A4.

In the atorvastatin development program, CPK levels were monitored in 2-week to 6-month intervals to ensure the patient's safety. A CPK value >10 × ULN at 2 consecutive measurements taken 4 to 10 days apart with muscle pain, tenderness, or weakness was considered clinically important.

No atorvastatin-treated patient in completed or ongoing studies had a clinically important CPK elevation. There were, however, patients with 1 CPK measurement >10 × ULN and concurrent muscle pain, tenderness, or weakness, as well as patients (in ongoing studies) with 2 CPK measurements >10 × ULN without concurrent muscle symptoms. The review of these safety data reveals that, in general, myopathic effects of atorvastatin are rare, as is the case with the other statins, are idiosyncratic in nature, with no apparent dose effect on incidence.

The review of CPK elevations associated with atorvastatin therapy will include first an analysis of maximum levels with respect to the upper limit of normal (ULN), and will include examination of the effect of dose as well as a comparison to the other HMGRIs studied in this clinical database.

Maximum CPK levels

The table below shows that for the fixed-dose data grouping overall, the vast majority of patients treated with in the combined atorvastatin and other HMGRI groups (~98%) had maximum CPK levels <3 x ULN. When the overall data are examined by dose of atorvastatin, there is a trend, at least from the 10 mg to the 80 mg group, in the incidence of maximum levels >3 x ULN. Specifically, 11/341 (3.2%) of patients in the 80 mg group compared to 34/2254 (1.2%) of patients in the atorvastatin 10 mg group had maximum CPK >3 x ULN. In addition, only 9/535 (1.7%) of patients in the combined HMGRI group had similar elevations. The incidence among placebo patients was 0.7%.

TABLE 8.8.7. Fixed-Dose Data Grouping: Maximum CPK Levels by Baseline CPK Level

CPK Values by Treatment Group/Dose at Screening/ Baseline	Number[a] of Patients	FIXED DOSE STUDIES Treatment Phase							
		≤3 × ULN		3-≤5 × ULN		5-≤10 × ULN		>10 × ULN	
≤3 × ULN									
Placebo	267	265	(99)	2	(1)	0	(0)	0	(0)
Atorvastatin (combined)	2223	2195	(99)	22	(1)	4	(0)	2	(0)
10.0 mg	1557	1540	(99)	13	(1)	3	(0)	1	(0)
20.0 mg	184	183	(99)	1	(1)	0	(0)	0	(0)
40.0 mg	75	73	(97)	1	(1)	1	(1)	0	(0)
80.0 mg	334	326	(98)	7	(2)	0	(0)	1	(0)
Combined HMG-CoA	531	522	(98)	6	(1)	3	(1)	0	(0)
>3 × ULN									
Placebo	0	0	(0)	0	(0)	0	(0)	0	(0)
Atorvastatin (combined)	31	25	(81)	2	(6)	3	(10)	1	(3)
10.0 mg	19	16	(84)	1	(5)	2	(11)	0	(0)
20.0 mg	2	2	(100)	0	(0)	0	(0)	0	(0)
40.0 mg	3	3	(100)	0	(0)	0	(0)	0	(0)
60.0 mg	0	0	(0)	0	(0)	0	(0)	0	(0)
80.0 mg	7	4	(57)	1	(14)	1	(14)	1	(14)
Combined HMG-CoA	4	4	(100)	0	(0)	0	(0)	0	(0)
All Values									
Placebo	267	265	(99)	2	(1)	0	(0)	0	(0)
Atorvastatin (combined)	2254	2220	(98)	24	(1)	7	(0)	3	(0)
10.0 mg	1576	1556	(99)	14	(1)	5	(0)	1	(0)
20.0 mg	186	185	(99)	1	(1)	0	(0)	0	(0)
40.0 mg	78	76	(97)	1	(1)	1	(1)	0	(0)
80.0 mg	341	330	(97)	8	(2)	1	(0)	2	(1)
Combined HMG-CoA	535	526	(98)	6	(1)	3	(1)	0	(0)

[a] Number of patients with both or baseline and posttreatment measurement.

In the analysis of the **all-completed studies** dataset, shown in the table below, again the vast majority of patients in placebo, combined atorvastatin, and combined HMGRIs groups had maximum CPK levels <3 x ULN. It is interesting, however, that the only levels >10 x ULN were in atorvastatin patients, with an incidence of 0.4% (11/2483). Three instances occurred in patients with CPK elevated at baseline, but 8 of 11 were in patients with normal baseline CPK. Of the 11 patients, only 3 had concurrent symptoms of muscle pain, tenderness, or weakness. One of the patients was a marathon runner who had recently completed a race. The distribution of these cases by dose of atorvastatin is shown in the second table below. There is no apparent dose-related increase in the incidence of maximum CPK levels for any of the intervals above normal listed in the table. This supports the idiosyncratic nature of the myopathic effects of this class of drugs (short of the known drug-drug interactions).

TABLE 8.8.8. All Completed Studies Data Grouping: Maximum CPK Levels by Baseline CPK Level

CPK Values by Treatment Group/Dose at Screening/ Baseline	Number* of Patients	ALL COMPLETED STUDIES Treatment Phase ≤3 × ULN	3-≤5 × ULN	5-≤10 × ULN	>10 × ULN
≤3 × ULN					
Placebo	108	106 (98)	2 (2)	0 (0)	0 (0)
Atorvastatin (combined)	2452	2390 (97)	39 (2)	15 (1)	8 (<1)
Combined HMG-CoA	730	707 (97)	16 (2)	7 (1)	0 (0)
>3 × ULN					
Placebo	0	0 (0)	0 (0)	0 (0)	0 (0)
Atorvastatin (combined)	31	24 (77)	3 (10)	1 (3)	3 (10)
Combined HMG-CoA	4	4 (100)	0 (0)	0 (0)	0 (0)
All Values					
Placebo	108	106 (98)	2 (2)	0 (0)	0 (0)
Atorvastatin (combined)	2483	2414 (97)	42 (2)	16 (1)	11 (0)
Combined HMG-CoA	734	711 (97)	16 (2)	7 (1)	0 (0)

* Number of patients with both a baseline and posttreatment measurement.

Table 8.8.9. Summary of maximum CPK levels by dose. All completed studies.

Dose	Number of patients*	>3≤5 x ULN	>5≤10 x ULN	>10 x ULN
0*	99	1 (1)	1 (1)	0 (0)
10	1395	20 (1)	6 (<1)	5 (<1)
20	366	6 (2)	3 (1)	2 (1)
40	204	6 (3)	5 (2)	1 (<1)
80	346	9 (3)	1 (<1)	3 (1)

*Number of patients is the number of patients whose maximum elevation was at the dose indicated, not the number of patients receiving that dose.
*Patient was on 0 dose at time of the event

Ongoing studies

One patient on atorvastatin 10 mg had a CPK level of 23,900 U/L on day 171 of treatment. The patient had previous completed another study and had a total atorvastatin exposure of 535 days. The CPK level fell to 2080 U/L by day 175 and to near normal 10 days later. There were no symptoms.

One lovastatin 80 mg patient had a clinically important CPK elevation first noted on day 85 of therapy and resolved by day 99.

Reviewer's comments on CPK abnormalities

The data reviewed suggest no extraordinary muscle toxicity for atorvastatin relative to the other HMGRIs, based both upon the head-to-head comparison trials as well as on historical data. Furthermore, neither the incidence of all elevations to greater than 3 X ULN nor the incidence of clinically important (persistent, marked, and symptomatic) elevations appears to be dose-related. The muscle effects of atorvastatin appear idiosyncratic in nature, consistent with other members of the class.

RCM # 2007-525
NDA 020687
ANDA 091178
Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2021

The following information is from United States (U.S.) post-marketing reports received by FDA of adverse events that occurred among patients who had taken mifepristone for medical termination of pregnancy. Because FDA has eliminated duplicate reports, and in some cases, reclassified the adverse event terms for individual cases after reviewing the narrative details, the numbers provided here may differ from the numbers of the reports that may be obtained through Freedom of Information Act requests. These events cannot with certainty be causally attributed to mifepristone because of information gaps about patient health status, clinical management of the patient, concurrent drug use, and other possible medical or surgical treatments and conditions. The estimated number of women who have used mifepristone in the U.S. for medical termination of pregnancy through the end of June 2021 is approximately 4.9 million women.

For informational purposes, fatal foreign cases that were reported after U.S. approval of mifepristone for medical termination of pregnancy are also included in a footnote in Table 1.

Table 1. Cumulative Post-Marketing Fatal and Ectopic Pregnancy Reports in U.S. Women Who Used Mifepristone for Medical Termination of Pregnancy

Date range of cumulative reports	09/28/00[†] - 06/30/21
Died [‡]	26
*Ectopic pregnancies [||]	97

[†] U.S. approval date

[‡] The fatal cases are included regardless of causal attribution to mifepristone. Deaths were associated with sepsis in eight of the 26 reported fatalities (seven cases tested positive for *Clostridium sordellii*, and one case tested positive for *Clostridium perfringens*). Seven of the eight fatal sepsis cases reported vaginal misoprostol use; one case reported buccal misoprostol use. Seventeen of the 18 remaining U.S. deaths involved two cases of homicide, two cases of combined drug intoxication/overdose, two cases of ruptured ectopic pregnancy, two cases of drug intoxication, and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; delayed onset toxic shock-like syndrome; hemorrhage; bilateral pulmonary thromboemboli; unintentional overdose resulting in liver failure; and a case of natural death due to severe pulmonary emphysema. In the eighteenth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. There were 12 additional reported deaths in women in foreign countries who used mifepristone for medical termination of pregnancy. These fatal cases were associated with the following: sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial; sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure;" thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; thromboembolism; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes, a jejunostomy feeding tube, and severe cystic fibrosis; and a case of *Clostridium septicum* sepsis (from a published literature report).

* The majority of these women are included in the hospitalized category in Table 2.

[||] Administration of mifepristone and misoprostol is contraindicated in patients with confirmed or suspected ectopic pregnancy (a pregnancy outside the uterus).

Table 2. Post-Marketing Adverse Events in U.S. Women Who Used Mifepristone for Medical Termination of Pregnancy		
Date ranges of reports received	09/28/00[†] - 10/31/12	11/01/12 - 06/30/21[‡]
Cases with any adverse event	2740	1467
Hospitalized, excluding deaths	768	277
*Experienced blood loss requiring transfusions [§]	416	187
Infections [||] (*Severe infections [¶])	308 (57)	105 (13)

[†] U.S. approval date

[‡] FDA implemented the FDA Adverse Event Reporting System (FAERS) on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. As a result of this change, it is not recommended to calculate a cumulative number when reviewing the data provided in Table 2.

* The majority of these women are included in the hospitalized category in Table 2.

[§] As stated in the approved labeling for Mifeprex (mifepristone) and its approved generic version, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days. Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.

[||] This category includes endometritis (inflammation resulting from an infection involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as chlamydia and gonorrhea, cystitis, and toxic shock syndrome not associated with a pelvic infection.

[¶] This subset of infections includes cases that were determined to be severe based on medical review of the available case details. Severe infections generally result in death or hospitalization for at least 2-3 days, require intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, or have other physical or clinical findings, laboratory data, or surgery that suggest a severe infection.

No. 23-10362

IN THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

ALLIANCE FOR HIPPOCRATIC MEDICINE; AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS; AMERICAN COLLEGE OF PEDIATRICIANS; CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS; SHAUN JESTER, D.O.; REGINA FROST-CLARK, M.D.; TYLER JOHNSON, D.O.; GEORGE DELGADO, M.D.,

Plaintiffs-Appellees,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, Commissioner of Food and Drugs; JANET WOODCOOK, M.D., in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration; PATRIZIA CAVAZZONI, M.D., in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, Secretary, U.S. Department of Health and Human Services,

Defendants-Appellants,

DANCO LABORATORIES, L.L.C.,

Intervenor-Appellant.

ADDENDUM TO EMERGENCY MOTION FOR A STAY PENDING APPEAL

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VOLUME II

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	SE-2 Efficacy Supplement
Application Number(s)	NDA 020687/S-020
Priority or Standard	Standard
Submit Date(s)	May 28, 2015
Received Date(s)	May 29, 2015
PDUFA Goal Date	March 29, 2016
Division / Office	(b) (6)
Reviewer Name(s)	(b) (6) and (b) (6)
Review Completion Date	March 29, 2016
Established Name	Mifepristone
(Proposed) Trade Name	Mifeprex
Therapeutic Class	Progestin antagonist
Applicant	Danco Laboratories, LLC
Formulation(s)	Oral Tablet
Dosing Regimen	For pregnancies through 70 days gestation: Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol.
Indication(s)	Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.
Intended Population(s)	Pregnant women who desire a medical termination through 70 days gestation.

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1 Recommendations/Risk Benefit Assessment

This NDA supplement from the Applicant, Danco Laboratories, LLC (called Danco or the Applicant throughout this clinical review), requested the following changes to the NDA for Mifeprex, approved 15 years ago in September 2000.

Changes proposed by the Applicant:

1. Change the dosing regimen: Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally
2. Remove the statement in labeling that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman.
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up needed, but not restricted to in-clinic at 14 days after Mifeprex
5. Increase the gestational age from 49 days to 70 days
6. Change the labeled time for expulsion of the products of conception from 4-24 hours to 2-24 hours post misoprostol administration
7. Add that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change “physician” to “(b) (4) in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change indication to add reference to use of misoprostol: “Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation.”
10. Remove references to “under Federal law” from the Prescriber’s Agreement
11. Address the Pediatric Research Equity Act (PREA) requirement for pediatric studies

Each of these 11 items will be discussed in the appropriate section of this review, generally under Section 6: Review of Efficacy and Section 7: Review of Safety. Four of the items, namely Number 8-11, are primarily regulatory and/or legal. They are discussed in Sections 1.3 and 9.4 (REMS recommendations and Prescriber’s Agreement), 7.6.4 (PREA), and 9.2 (Labeling recommendation). Additional information is found in Section 7.7 (2) on the change to “(b) (4) Section 7.7 (3) on “under Federal law”, and Section 7.7 (4) on the reference to use of misoprostol.

1.1 Recommendation on Regulatory Action

The clinical reviewers recommend an approval action for this efficacy supplement.

1.2 Risk Benefit Assessment

1. Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally.

   The Applicant has submitted sufficient evidence from the published medical literature to demonstrate that decreasing the dose of Mifeprex from 600 mg to 200 mg while increasing the dose of misoprostol from 400 to 800 mcg is safe and efficacious for termination of pregnancy through 70 days gestation. The risk/benefit balance favors approval.

   There is sufficient evidence that a dosing regimen with buccal administration of 800 mcg misoprostol is safe and effective. This change in the dosing regimen should be approved.

2. Allow administration of misoprostol outside of the clinic:

   Based on the evidence submitted by the Applicant, a dosing regimen that includes administration of misoprostol outside of the clinic is safe and effective for termination of pregnancy through 70 days gestation; labeling should be revised to remove the requirement for in-clinic dosing of misoprostol

3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex:

   The available evidence supports that a dosing regimen that provides for administration of misoprostol 24-48 hours after administration of Mifeprex is safe and effective. The risk/benefit assessment demonstrates that this change in the dosing regimen should be approved.

4. Follow-up needed, but not restricted to in-clinic at 14 days after Mifeprex:

   Based on the evidence submitted by the Applicant supporting this change, flexibility in timing and method of follow-up after medical abortion is safe. Labeling should be revised to remove the requirement for in-clinic follow-up at 14 days.

5. Increase the gestational age from 49 days to 70 days:

   As detailed in the following review, the Applicant has submitted sufficient evidence for the safety and efficacy of medical abortion with Mifeprex, in a regimen with misoprostol, through 70 days gestation. The risk/benefit assessment supports the approval of the new dosing regimen up through 70 days gestation.

6. Change the labeled time for expulsion of the products of conception from 4-24 hours to 2-24 hours post misoprostol administration:

   The Applicant has submitted sufficient data from the published medical literature to support approval of a change in the label to note time to expulsion ranges from 2-24 hours.

7. Add that a repeat 800 mcg buccal dose of misoprostol may be used if needed:

The Applicant has submitted sufficient evidence to support that a repeat dose of misoprostol may be used through 70 days gestation to complete expulsion of the products of conception if needed. The risk/benefit assessment supports approval of this change. There have been rare reports of uterine rupture with use of misoprostol in women with prior uterine scar(s). This information should be added to the Mifeprex label.

8. Change "physician" to "(b) (4) in the labeling and Risk Evaluation and Mitigation Strategies (REMS) document:

   The Applicant has submitted sufficient data to support that Mifeprex is safe and effective when prescribed by midlevel practitioners as well as by physicians. Therefore, the term "licensed physician" was changed in the label and REMS materials to "healthcare provider who prescribes." This broader category of providers will still have to meet the certification criteria specified in the Prescriber Agreement Form.

9. Change the approved indication to add reference to use of misoprostol: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation." Based on current Agency labeling practice regarding drugs used together in a treatment regimen, the addition of misoprostol to the Indication Statement for Mifeprex should be approved.

10. Remove references to "under Federal law" from the Prescriber Agreement:

    The Agency has determined that there is no precedent for using this phrase in other REMS, nor is there any clinical rationale for including it; therefore, it is acceptable to remove "under Federal law" from the Prescriber Agreement Form.

11. Address the Pediatric Research Equity Act (PREA) requirement for pediatric studies:

    The Applicant has submitted sufficient evidence from the published medical literature to address the PREA requirement for this supplemental application. The Applicant has demonstrated that Mifeprex is safe and effective in postmenarchal females, including those under 17 years of age. (b) (6) concurred with granting a partial waiver under PREA in patients ages birth to 12 years of age who are premenarche.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Changes proposed in this efficacy supplement entailed a number of modifications to the current Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex. See Section 9.4 for full details. The (b) (6) ((b) (6) concurs with the (b) (6) ((b) (6) evaluation of the REMS modifications, which include:

- Removal of "under Federal law" from the Prescriber Agreement Form is acceptable (see discussion in Additional Submissions / Issues).
- The term "healthcare providers who prescribe" is preferable to the Applicant's proposed "(b) (4) (see discussion in Additional Submissions / Issues).
- It is appropriate to modify the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." Under these requirements, healthcare providers report certain adverse events to the Applicant, which then is required to report the adverse events to FDA. FDA has received such reports for 15 years, and it has determined that the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely. For this reason, ongoing reporting by certified healthcare providers to the Applicant of all of the specified adverse events is no longer warranted. . It should be noted that the Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience reports.

(b) (6) concurs with the following modifications recommended by (b) (6)

- Removal of the Medication Guide (MG) from the REMS. The MG will remain a required part of labeling and will be required to be provided to patients consistent with the requirements in 21 CFR part 208. FDA has been maintaining MGs as labeling but removing them from REMS when, as here, inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks, such as when the MG is redundant and not providing additional use or information to the patient about the risk(s) the REMS is intended to mitigate. This is consistent with ongoing efforts to streamline REMS by allowing for updates to the MG without need for a REMS modification.
- Removal of the Patient Agreement form (ETASU D). This decision was based on the well-established safety profile of Mifeprex, as well as the fact that the small numbers of practitioners who provide abortion care in the US use informed consent practices that are duplicated of the current Patient Agreement and thus the Patient Agreement is no longer necessary to ensure that the benefits of the drug outweigh the risks.
- Revision of the Prescriber Agreement Form to reflect changes to labeling revisions pursuant to the proposed efficacy supplement, and to improve the flow of the document.
- Revision of the REMS goals to reflect the above changes

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for postmarket requirements or commitments for this efficacy supplement.

2 Introduction and Regulatory Background

2.1 Product Regulatory Information

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' (7 weeks) pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments." Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets certain qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments that the then-applicant of the Mifeprex NDA (i.e., the Population Council) agreed to meet:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on Day 14 (compliance with return visit) were incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.
2. A surveillance study on outcomes of ongoing pregnancies.

In addition, the 2000 approval letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco).

2.2 Tables of Currently Available Treatments for Proposed Indications

In the US there are no other approved products for the medical termination of first trimester pregnancy. Misoprostol alone or in combination with methotrexate has been used for early medical abortion (MAB), with much lower success than Mifeprex.[1]

[1] American College of Obstetricians and Gynecologists. Practice bulletin No. 143: medical management of first-trimester abortion. Obstet Gynecol 2014;123(3):676-92. doi:10.1097/01.AOG.0000444454.67279.7d.

2.3 Availability of Proposed Active Ingredient in the United States

Mifepristone: The only other FDA approval for mifepristone is the product Korlym, approved under NDA 202107 on February 17, 2012 for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

2.4 Important Safety Issues with Consideration to Related Drugs

Korlym (mifepristone) is indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. Korlym is taken in oral doses of 300 mg to 1200 mg daily. It is contraindicated in pregnancy, patients taking simvastatin, lovastatin and CYP3A substrates with narrow therapeutic ranges, patients on corticosteroids for lifesaving purposes, and women with unexplained vaginal bleeding or endometrial hyperplasia with atypia or endometrial carcinoma. The label[2] provides warnings and precautions regarding adrenal insufficiency, hypokalemia, vaginal bleeding and endometrial changes, QT prolongation, exacerbation or deterioration of conditions treated with corticosteroids, use of strong CYP3A inhibitors, and opportunistic infections with *Pneumocystis jiroveci* pneumonia in patients with Cushing's. Adverse reactions noted in ≥20% of patients in clinical trials with Korlym included nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite and endometrial hypertrophy.

Reviewer comment:

Some of the adverse events noted with Korlym are also seen with Mifeprex, such as nausea and vomiting. However, Korlym is taken in higher doses, in a chronic, daily fashion unlike the single 200 mg dose of Mifeprex that is the subject of this supplement; the rate of adverse events with Mifeprex is much lower.

Ella (ulipristal acetate) is a progesterone agonist/antagonist emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. The **ella** label[3] notes that in clinical trials, the most common adverse reactions (≥ 10%) in women receiving **ella** were headache (18% overall) and nausea (12% overall) and abdominal and upper abdominal pain (12% overall).

Due to **ella's** high affinity binding to the progesterone receptor, use of **ella** may reduce the contraceptive action of regular hormonal contraceptive methods. The label notes that after **ella** intake, menses sometimes occur earlier or later than expected by a few

[2] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202107s000lbl.pdf

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf

days. In clinical trials, cycle length was increased by a mean of 2.5 days but returned to normal in the subsequent cycle. Seven percent of subjects reported menses occurring more than 7 days earlier than expected, and 19% reported a delay of more than 7 days. The label recommends that women rule out pregnancy if the expected menses is delayed by more than one week. Nine percent of women studied reported intermenstrual bleeding after use of **ella**.

Reviewer comment:

Ella is for occasional use and is not to be used as a regular contraceptive method. As such, the drug is not recommended for repeated use in the same menstrual cycle. The safety and efficacy of repeat use within the same cycle has not been evaluated. A single dose of ella does not appear to result in serious adverse events.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-NDA meeting was held with the Applicant on January 29, 2015. The following items, among others, were discussed:

- New dosing regimen
- Proposal to have (b) (4)
- Use up to (b) (4) days' gestation
- Change in the interval between Mifeprex and misoprostol administration to 24-48 hours
- Revision of the labeled time to expulsion after misoprostol is administered
- Use of the term "(b) (4) in the approval and label to describe who may obtain and dispense Mifeprex
- Deletion of "under Federal law" in the Prescriber's Agreement
- PREA requirements
- Regulatory pathway for approval

2.6 Other Relevant Background Information

Since the approval in France and China in 1988, mifepristone for MAB is currently approved in 62 countries globally[4]; see the list and dates of approval in Appendix 9.7.

Prior to the Mifeprex approval by the FDA, mifepristone had also been approved in the UK in 1991. In the UK, the current therapeutic indications include:

- Medical alternative to surgical termination of intrauterine pregnancy up to 63 days gestation based on the first day of the last menstrual period
- Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination during the first trimester

[4] Gynuity website, www.gynuity.org, Medical Abortion in Developing Countries- List of Mifepristone Approvals.

- For use with prostaglandin analogues for termination of pregnancy for medical reasons beyond the first trimester
- Labour induction in foetal death in utero[5]

The estimated cumulative use of Mifeprex in the US since the 2000 approval is 2.5 million uses. Estimated global occurence of MAB and SAB combined was 43.8 million abortionsin 2008 (Guttmacher Institute data)[6]. MAB has been increasingly used as its efficacy and safety have become well-established by both research and experience, and serious complications have proven to be extremely rare.[7] Medical abortion comprises 16.5% of all abortions in the US, 25.2% of all abortions at or before 9 weeks of gestation[1], and based on data from 40 reporting areas sending data to the CDC, 30.8% of all abortions at or before 8 weeks gestation (2012 data).[8] In 2011, approximately 239,400 medical abortions were performed, which was a 20% increase from 2008 data.[9] Data show that in the most recently reported 12 months (September 29, 2014-September 28, 2015), (b) (4) Mifeprex tablets were distributed in the US (NDA 20687 SD # 650, Annual Report-15, submitted October 09, 2015). Further, the vast majority of practitioners in the US who provide medical abortion services use a regimen other than the FDA-approved one. In 2008, Wiegerinck et al published a survey of members of the National Abortion Federation which showed that only 4% of facilities were using the current FDA-approved regimen.[10]

It is noteworthy that ten years ago, the combination of mifepristone and misoprostol for medical abortion was included on the World Health Organization (WHO) Model list of Essential Medicines for termination of pregnancy where legal and acceptable, up to 9 weeks of gestation.[11] Several other national and international organizations have also endorsed the safe use of medical abortion up to 9 and 10 weeks of gestation. This topic will be discussed thoroughly in the Efficacy and Safety Sections.

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[5] Mifegyne Summary of Product Characteristics. Exelgyn Laboratories- June 2013. *https://www.medicines.org.**uk**/emc/medicine/617*

[6] Sedgh G et al., Induced abortion: incidence and trends worldwide from 1995 to 2008. Lancet, 2012;379:625-32.

[7] Cleland K, Smith N. Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data. Contraception 2015;92:179-81.

[8] Pazol K, Creanga AA, Zane SB, Burley KD, Jamieson DJ. Abortion surveillance--United States, Centers for Disease Control and Prevention (CDC). MMWR Surveill Summ 2012;61(SS-8):1–44 and Surveillance Summaries Nov 27, 2015; 64(SS10);1-40.

[9] Jones RK, Jerman J. Abortion incidence and service availability in the United States, 2011. Perspectives on Sexual and Reproductive Health 2014;46(1):3-14.doi10.1363/46e0414.

[10] Wiegerinck MMJ, Jones HE, O'Connell, K, Lichtenberg ES, Paul M, Westhoff CL. Medical abortion practices: a survey of National Abortion Federation members in the United States. Contraception 2008;78:486-491.

[11] World Health Organization April 2015 Model Lists of Essential Medicines Available online at http://www.who.int/medicines/publications/essentialmedicines/en/.

MAB is a choice that women have available in many areas, especially urban, in the US, although it should be noted that some geographical areas in the US have very limited availability of both the surgical and medical options or even one option for early pregnancy termination.

The primary advantages of having a MAB compared to a surgical abortion (SAB) are the following:

- Limited or no anesthesia
- Limited likelihood of any surgical intervention

Reviewer's Comment:

A very small number of physicians currently provide early medical terminations. In the most recent REMS update from the Applicant (stamp date June 3, 2015), the cumulative number of certified prescribers since 2000 is only (b) (4). Between May 1, 2012 and April 30, 2015, the number of new prescribers was (b) (4) and the number of prescribers ordering Mifeprex was (b) (4) during this 3-year period. The number of healthcare providers that are performing early SAB is not documented.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Because this submission did not rely on datasets from any of the clinical trials, no FDA inspections were performed at clinical sites. The authors of the numerous articles, however, have published widely in peer-reviewed medical journals.

3.2 Compliance with Good Clinical Practices

This submission relies on findings from the published medical literature. The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent.

3.3 Financial Disclosures

None were submitted or required.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

On March 10, 2016, a separate supplement approved the packaging of a single 200 mg tablet of mifepristone compared to the current 3 tablets in a blister pack. Each packet will have an individual barcode.

Reviewer comment:

The approval of single tablet packaging should make recording the barcode of the mifepristone tablet in the patient record (as provided in the REMS) easier as the new proposed dosing regimen uses only one 200 mg mifepristone tablet compared to the previously approved regimen of three tablets.

(b) (6), reviewed the PLR conversion of the label. Her review, dated January 11, 2016 states the following:

> "No changes have been made in the approved chemistry, manufacturing and controls. The approved 200 mg tablet will be used. This review evaluates the PLR conversion of the labeling. Sections 3, 11, and 16 of the PLR labeling, and the Highlights of Prescribing Information, have been evaluated from a chemistry perspective.
>
> **Overall Evaluation**: Acceptable. The labeling provided in Section 3, Section 11, and Section 16, and the Highlights of Prescribing Information, is identical in content to the approved information. The PLR conversion labeling, therefore, is acceptable from a chemistry perspective. The PLR label also corresponds to the content and format required in 21 CFR 201.57.

Reviewer comment:

We agree with the conclusions in the CMC review of the PLR conversion of the label.

4.2 Clinical Microbiology

The chemistry (CMC) reviewers determined that a microbiology review was not needed for this efficacy supplement.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology review by (b) (6), dated March 2, 2016. No preclinical data were submitted for this efficacy supplement.The reviewer's only recommendations were labeling changes. His comments were conveyed to the Sponsor.

Per (b) (6) review, the supplement is approvable from a Pharmacology/Toxicology standpoint.

4.4 Clinical Pharmacology

The Clinical Pharmacology review by (b) (6) concluded with the following recommendation:

> "(b) (6), (b) (6) has reviewed the available clinical pharmacology information in relation to the newly proposed regimen for Mifeprex®. We find the application to be acceptable from a Clinical Pharmacology perspective, provided that an agreement on the language in the package insert is reached between the Sponsor and the Division."
>
> No postmarketing commitments or requirement are recommended.

4.4.1 Mechanism of Action

The original approved label states:

> "The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.
>
> …..During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins."

4.4.2 Pharmacodynamics

No new studies were submitted with this Application. See the original approved label.

4.4.3 Pharmacokinetics

(b) (6) review states the following:

> The pharmacokinetics (PK) of 200 mg mifepristone tablet has not been characterized in women. However, the PK data of 200 mg mifepristone tablet in men are available (1996 study): the mean maximum concentration (C_{max}) (± standard error) = 1.77 (±0.23) mg/L, the mean time to reach C_{max} (T_{max}) = 0.81 (±0.16) hour, and the mean area-under-the curve (AUC) = 25.8 (±2.2) mg·h/L. While the effects of sex on the disposition of mifepristone have not been evaluated using Mifeprex®, no sex differences in PK of mifepristone were seen with 300 mg mifepristone in a different NDA review (Korlym™, NDA 202107, Clinical Pharmacology review). Therefore, Section 12.3 of the proposed label in a PLR format should include the available PK data of mifepristone 200 mg tablet.
>
> Cytochrome P450 3A4 (CYP3A4) plays an important role in the metabolism of mifepristone. Therefore, concomitant intake of CYP3A4 inducers with mifepristone

is anticipated to have a significant effect on the disposition of mifepristone. However, the Sponsor did not conduct any *in vivo* studies to evaluate the effect of CYP3A4 inducers on the PK of Mifeprex®. Although the lowest effective therapeutic margin of mifepristone for termination of pregnancy has been not characterized clearly, the use of misoprostol in the regimen for Mifeprex® contributes to efficacy for inducing termination of pregnancy. In addition, concomitant intake of CYP3A4 inducers does not appear to affect the systemic exposure of misoprostol. In the proposed new regimen, another dose of misoprostol can be administered following day 7 to 14 of post-treatment of mifepristone if termination of pregnancy does not occur.

In summary, the contribution of misoprostol in termination of pregnancy and additional dosing option of misoprostol may compensate the possibly diminished efficacy of Mifeprex® in the users of CYP3A4 inducers. However, the labeling information should include the practical clinical guidance for the subject who has been exposed to CYP3A4 inducers.

Reviewers comments:

- **We agree with the Clinical Pharmacology conclusions and recommendations made by (b) (6).**

- **Within the last 10 years, administration of oral mifepristone followed by buccal misoprostol for early medical abortion has become the standard of care for MAB in many countries, including the US. This is based on 1) the PK profile of different doses and routes of administration for misoprostol, and 2) many clinical trials comparing the efficacy and safety of different dosing regimens.**

From Chen and Creinin (2015)[12]:

"With buccal administration, misoprostol is held in the buccal pouch between the teeth and gums for 30 minutes before swallowing any remaining tablets. Buccal misoprostol is slowly absorbed, unlike oral misoprostol, which is rapidly absorbed and undergoes extensive first-pass metabolism. After a dose of oral misoprostol, plasma misoprostol acid levels peak quickly at 30 minutes and decrease rapidly by 120 minutes. In contrast, after buccal administration, plasma misoprostol acid levels rise gradually to peak concentration after a median time of 75 minutes and fall slowly over several hours."

[12] Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015;126(1):12-21.

The PK profile of vaginal misoprostol is very similar to that of buccal misoprostol. These pharmacological differences between vaginal and buccal misoprostol do not have a clinically meaningful effect on the efficacy at different gestational weeks and the adverse event profile for the combination of mifepristone and misoprostol for early medical abortion. Those routes with rapid and significant absorption (e.g., sublingual) also have high efficacy (ACOG Bulletin[1]). This review, however, focuses primarily on the new dosing regimen proposed by the Applicant with some supportive data from studies that used vaginal and sublingual misoprostol.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were many studies that provided data for this NDA review. The original US trial that was reviewed for the Mifeprex approval in 2000 was performed over 20 years ago in 1994-95. Subsequently, there has been 20 years of experience with MAB, guidelines from professional organizations here and abroad, and clinical trials that have been published in the peer-reviewed medical literature. This review focuses on the information submitted by the Applicant for the change in the dosing regimen and follow-up.

For a complete list of all sources of information, see the extensive list of references in Appendix 9.6 at the end of this review.

Table 1: List of Major Studies Reviewed

USA	International
Gatter 2015[13], retrospective	Louie 2014[14], Azerbaijan, prospective
Ireland 2015[15], retrospective	Ngoc 2014[16], Vietnam, prospective
Chong, 2015[17], prospective single-arm	Raymond 2013[18], International, including US, retrospective
Winikoff 2012[19], prospective	Goldstone 2012[20], Australia, retrospective
Perriera 2010[21], prospective	Boersma 2011[22], Curacao, prospective
Winikoff 2008[23], RCT*	Middleton 2005[24], prospective
Creinin 2007[25], prospective	Spitz 1998[26], single arm trial

[13] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.

[14] Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. Eur J Contracept Reprod Health Care 2014;19(6):457-464.

[15] Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. Obstet Gynecol 2015;126:22-8.

[16] Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. Obstet Gynecol 2014;123:88-95.

[17] Chong E, Frye LJ, Castle J, Dean G, Kuehl L, Winikoff B. A prospective, non-randomized study of home use of mifepristone for medical abortion in the US. Contraception 2015;92:215-291.

[18] Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.

[19] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012;120:1070-6.

[20] Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. Med J Austral 2012; 197: 282-6.

[21] Perriera LK, Reeves MF, Chen BA, Hohmann HL, Hayes J, Creinin MD. Feasibility of telephone follow-up after medical abortion. Contraception 2010;81:143-149.

[22] Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011;16:61-6.

[23] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008;112(6):1303-1310.

[24] Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005;72:328-32.

[25] Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Medical Abortion at the Same

Source: compiled by clinical reviewers. *Randomized controlled trial.

Reviewer's comment:

Table 1 **above lists the major studies and review articles covering over 45,000 women who had an early MAB through 70 days gestation. Both retrospective and prospective studies were found to be valuable for this review. There are additional studies submitted by the Applicant that are not quoted or reviewed primarily because they did not use a dosing regimen relevant to that proposed by the Applicant or did not contain information pertinent to the other requested changes (e.g., less restrictive follow-up requirements or gestations through 70 days) in the NDA supplement. In some cases, studies that used variants of the proposed regimen were considered because PK, PD and clinical data indicate the relevance of data on vaginally-administered misoprostol, and because lower doses and certain other routes of administration of misoprostol are expected to have lower or similar levels of effectiveness.**

5.1.1 Submissions during the Review Process

During the course of the review, the Applicant submitted additional supportive articles from the peer-reviewed medical literature, and provided more detailed data from previously submitted articles based on direct communication with the authors. Further, the Applicant submitted changes to some of the original proposals. Below in Table 2 is a list of the clinical submissions to the NDA after the initial submission dated May 18, 2015.

Time (MAST Study Trial Group). Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion a randomized controlled trial. Obstet Gynecol 2007;109:885-894.

[26] Spitz IM, et al. Early Pregnancy Termination with Mifepristone and Misoprostol in the United States. NEJM 1998;338(18):1241-47.

Table 2 Clinical Submissions during the Course of the Review

Item	Submission Type, Date
Additional supportive articles More detailed data from previously submitted articles	Amendment # 3, dated 9/23/2015 Amendment # 4, dated 10/13/2015 Amendment # 5, dated 11/16/2015 Amendment # 6, dated 12/8/2015
Additional supportive documents on patient counseling	Follow-up to 1/27/2016 teleconference, dated 2/2/2016
Additional supportive articles	Amendment # 8, dated 2/25/2016
Proposed Additional Changes	
REMS amendment, Revised REMS Supporting Document Additional supportive articles	Amendment # 2, dated 7/16/2015
REMS modification	Dated 11/4/2015
Labeling: (b) (4) Indication Statement	Amendment # 4, dated 10/13/2015
Labeling changes: (b) (4) the proposed new dosage regimen (b) (4)	Follow-up to 1/27/2016 teleconference, dated 2/15/2016, Also in Amendment # 9, dated 2/25/2016
Labeling: changes to Sections 2.4, 5.2, 6.1, 7, 8.1, 8.2, 8.6, 12.3, 14	Amendment # 7, dated 2/23/2016
Labeling changes: revise indication statement to state “through 70 days gestation	Amendment # 9, dated 2/25/2016
Labeling: changes to Sections 2.3, 6.1 and 14	Amendment # 10, dated 3/17/2016
REMS documents	Amendment #11, dated 3/21/2016

Source: Reviewer table.

5.2 Review Strategy

This is a joint review by two medical officers: (b) (6) reviewed the efficacy data and (b) (6) reviewed safety data and related issues. Other sections are jointly completed.

Within the last 10 years, use of buccal misoprostol with mifepristone for MAB has become commonplace. However, the published literature did not contain abundant information about medical abortion outcomes with buccal misoprostol at the time of the

original NDA review. In this review, we summarize clinical outcomes and adverse effects of medical abortion regimens consisting of oral mifepristone 200 mg followed in 24-48 hours by buccal misoprostol 800 mcg in pregnancies through 70 days of gestation.

5.2.1 Discussion of Individual Studies/Clinical Trials

Information and findings from individual clinical trials and reviews in the published medical literature, websites, the Applicant and other sources are discussed in different sections throughout this review. As acknowledged during pre-submission discussions between the Applicant and (b) (6) and as is typical for literature-based submissions, original datasets from the trials that are cited were not available for submission in this supplement.

6 Review of Efficacy

Efficacy Summary

This summary lists the final conclusions based on review of the data. Not all of the conclusions, regarding covariates such as ethnicity, parity, previous abortion, are specifically addressed in labeling, but the reviewers believe that it is important to show that we evaluated many different aspects and potential risk factors for safe and effective MAB:

- Medical termination of pregnancies through 70 days gestation is safe and effective and should be approved using the new proposed regimen.
- The original approved dosing regimen remains safe and effective but the new proposed dosing regimen is effective and should be approved for use in gestations through 70 days (10 weeks) gestation.
- 2015 Chen-Creinin review[12] of over 33,800 MABs concluded that regimens with a 24-hour time interval between mifepristone and buccal misoprostol administration are slightly less effective (94.2% success) compared to those with a 24-48-hour interval (96.8% success).
- 2013 Raymond review[18] of over 45,500 MABs using oral mifepristone 200 mg and various misoprostol doses concluded that the effectiveness decreases when:
    - misoprostol is taken orally compared to the three other routes of administration (buccal, sublingual, or vaginal)
    - the gestational age increases
    - the mifepristone-misoprostol interval is less than 24 hours
    - the total misoprostol dose is 400 mcg or less
- Efficacy in the adolescent population is the same or slightly better compared to non-adolescent women.

- Efficacy outcomes do not appear to be related to other baseline characteristics including age, race, body weight, gravidity and previous spontaneous abortions. (Spitz data[26] and many subsequent studies)
- Data from the original US trial (1994-95; Spitz 1998[26]) showed lower efficacy rates with the originally approved Mifeprex dosing than is reported in a large number of subsequent trials using different mifepristone-misoprostol dosing regimens for early MAB. There does not appear to be any change in the safety profile.
- Raymond (2013 systematic review[18]) found no significant association between abortion failure rates and the timing of the follow-up evaluation.
- Over 30% of women will completely expel the products of conception within 4-5 hours of taking the misoprostol for MAB with gestations of 57-70 days (Winikoff 2012[19]); this finding supports the proposal to allow women to choose the timing of (within the labeled range) and where to take the misoprostol.
    - Data from the original NDA review showed occurrence of a successful (complete) MAB occurred in ≤ 4 hours after misoprostol administration in 45-46% of women up to 56 days gestation and 34.9% of women at 57-63 days gestation.
- Home administration of misoprostol is efficacious, practical, and safe (see Safety Section)

Reviewer's overall comment:

Compared to the current Mifeprex approved label and regimen, the Applicant has requested less restrictive measures for location and timing of misoprostol administration and follow-up measures for early MAB. We believe that a regimen that includes these less restrictive measures is equally safe and effective, while offering women greater convenience and providing a less burdensome procedure for patients and providers.

6.1 Indication

In the initial submission of this efficacy supplement, the proposed new indication was the following: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (b) (4)" In Amendment # 9, submitted on February 25, 2016, the Applicant proposed (b) (4) the gestational age through 70 days.

The proposed new modified regimen uses buccal (not oral) misoprostol administered 24-48 hours after taking a lower dose, 200 mg instead of 600mg, of oral mifepristone. The labeled dose of misoprostol is increased compared to the current approved regimen, from 400 mcg to 800 mcg. (b) (4) , the

(b) (4)
.

These requests were thoroughly reviewed by the Agency and we believe the product is safe and effective for the indication, which reads:

> "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation."

6.1.1 Methods

There were numerous articles from the peer-reviewed medical literature that were submitted by the Applicant. Articles were also cited in three letters sent to CDER Center Director Janet Woodcock, MD from 1) ACOG, 2) a group of academic professionals and women's health non-profit organizations, and 3) thirty professional and academic organizations, all of which requested changes to the Mifeprex labeling and REMS. All relevant publications cited in those three letters were also submitted by the Applicant for our review. The articles and sources of data used for this review are listed in the Reference List in Appendix 9.6 at the end of this review.

The various studies noted in the articles had slightly different designs, inclusion criteria, dosing regimens and endpoints for safety and efficacy. The review focus is on clinical trials and follow-up methods for early medical abortion, including gestations through 70 days (10 weeks).

6.1.2 Demographics

Many of the trials were randomized and some were blinded to the actual dose of the two drugs that were administered. The route of misoprostol administration could not be easily blinded. Although there may have been some small differences in the demographic data for the different arms, it is doubtful that demographic differences such as race or ethnicity are clinically meaningful in relation to the safety and efficacy of medical abortion.

6.1.3 Subject Disposition

Most of the studies noted the number of women who were lost to follow-up and did not count them in the efficacy analysis. All women with any available safety data were included in the safety analyses. See Safety Section for further discussion.

6.1.4 Analysis of Primary Endpoint(s)

The studies analyzed for data used in this NDA review almost universally defined their primary efficacy endpoint as expulsion of the pregnancy from the uterus without need for any surgical evacuation or procedure for any reason (including patient request).

6.1.5 Analysis of Secondary Endpoints(s)

In addition to the final outcome of MAB success or lack of success (i.e., surgical or medical intervention needed), there are intermediate outcomes:

- Incomplete abortion: pregnancy no longer ongoing, but only partial or non-expulsion of the products of conception has occurred
- Ongoing pregnancy based on fetal heartbeat and/or growth

In the case of incomplete expulsion but where the pregnancy is no longer ongoing, there are in the US several safe options available to the healthcare provider and the patient:

- Expectant management (in many cases, complete expulsion will occur spontaneously given additional time)
- Additional dose of misoprostol
- Minor surgical procedure such as a vacuum aspiration in the clinic/office
- Surgical procedure under anesthesia such as a dilation and curettage (D&C)

For ongoing pregnancies following the initial MAB procedure, typically one of the surgical procedures is performed.

In addition to these two intermediate outcomes, there are other cases in which a surgical intervention might be performed:

- Intervention because of bleeding or other aspect of the patient's condition: the healthcare provider judges that surgical intervention is indicated
- Patient request: the patient requests surgical intervention for any reason

6.1.6 Proposal for a New Dosing Regimen

There are five major changes proposed by the Applicant in this supplement for which efficacy data will be discussed. The changes are interrelated and, in general, the same studies usually provide evidence to support multiple changes, although data from a given study may be more or less pertinent to a specific change (e.g., extending the approved gestational age, home administration of buccal misoprostol, etc.).

Summary of changes to dosing regimen, indication, and follow-up initially requested by the Applicant in the NDA Supplement:

1. **Addition of a new dosing regimen of Mifeprex 200 mg orally followed by the buccal administration of 800 mcg misoprostol at 24-48 hours instead of 48 hours**

2. **Increase in gestational age from (b) (4)**

3. **Option to administer misoprostol outside of the clinic**

4. **Option that a repeat dose of misoprostol may be used if needed for women using the new proposed dosing regimen**

5. **Follow-up timing and methods: follow-up is needed at 7-14 days after Mifeprex administration; the specific nature and timing of the follow-up to be agreed upon by the (b) (4) and patient. The current approved label states: "Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex."**

Discussion and analysis of the data supporting the five changes follows in five individual sections.

1. **Proposal of a new dosing regimen that:**

   1) decreases the oral dose of Mifeprex from 600 mg to 200 mg orally,

   2) increases the misoprostol dose from 400 mcg orally to 800 mcg misoprostol administered buccally, and

   3) revises the interval between Mifeprex and misoprostol dosing from 48 hours to "24-48 hours."

(b) (4)

Background on some dosing data and US practices:

There is ample medical evidence that the currently approved dose regimen (oral mifepristone 600 mg followed 2 days later with oral misoprostol 400 mcg) is safe and efficacious up to 49 days gestation. It was approved in September 2000 based on the US clinical trial of 1994-95 and two French trials. After 1995, however, more studies gradually became available using lower doses of mifepristone and different doses and routes of administration for misoprostol. These newer data were not submitted to or considered in the original NDA review. Studies also showed that with lower doses (< 600 mg) of oral mifepristone followed by oral misoprostol 400 mcg, the treatment success rate is greater than 95% up to 49 days gestation.

It is difficult to tell how many MABs in the US actually used the FDA-approved dosing regimen following the 2000 approval. It is clear that many clinics and individual practitioners did not. For example, from 2001 to March 2006, Planned Parenthood Federation of America (PPFA) health centers throughout the United States provided medical abortions principally using a regimen of oral mifepristone 200 mg, followed 24–48 hours later by 800 mcg misoprostol administered vaginally at home.[27] Of note, PPFA has been and continues to be the largest provider of MAB services in the US.

[27] Fjerstad M, Sivin I, Lichtenberg ES, Trussell J, Cleland K, Cullins V. Effectiveness of medical abortion

Reviewer's comment:

The 2009 Fjerstad article[28] states that PPFA was a federation of 97 independent local affiliates operating 880 health centers throughout the US; roughly 300 of those centers provided medical abortion. So, within one year of the FDA Mifeprex approval, PPFA was using a dosing regimen (actual doses and routes of administration) very similar to that proposed in this efficacy supplement.

Meanwhile, from September 2003 to June 2005, there were four fatalities in the US and one in August 2001 in a Canadian clinical trial, all due to a sudden and rapid sepsis secondary to the bacteria *Clostridium sordellii*. The five cases were with early MAB (all around 7 weeks gestation) in women who had used 800 mcg vaginal misoprostol. By late March 2006, consideration of these fatal uterine infections led PPFA to 1) change the route of administration of the 800 mcg misoprostol from vaginal to buccal (or, much less commonly, oral) and 2) employ additional measures (sexually transmitted infection [STI] testing and treatment if positive, or use of prophylactic antibiotics) to minimize the risk of subsequent serious uterine infections. In July 2007, PPFA began requiring routine treatment with antibiotics for all medical abortions at their health centers.[28]

Reviewer's comment:

As stated in currently approved labeling "No causal relationship between the use of Mifeprex and misoprostol and these events [serious and sometimes fatal infections and bleeding] has been established." There is no clear evidence that the vaginal use of misoprostol causes infection, and no causal association has been identified between the cases of sepsis and vaginal administration of misoprostol. While labeling was revised in November 2004 and July 2005 to recommend that providers have a high index of suspicion in order to rule out serious infection and sepsis, the Agency did not consider there was sufficient evidence to justify recommending prophylactic antibiotics.

A 2006 article showed that in pregnancies greater than 49 days gestation, compared to oral administration of misoprostol, the bioavailability and efficacy with use of misoprostol is increased by vaginal, sublingual and buccal administration, avoiding first-pass metabolism by the liver.[29] Furthermore, a 2009 review of MAB[30] noted that:

> "Consistent with other kinetic studies, clinical trials have demonstrated no change in efficacy when mifepristone doses are reduced from 600 to 200 mg. Multiple

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with mifepristone and buccal misoprostol through 59 gestational days. Contraception 2009;80:282-6.

[28] Fjerstad M, Trussell J, et al. Rates of serious infection after changes in regimens for medical abortion. NEJM 2009;361:145-51.

[29] Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with prostaglandin analogue. Contraception 2006;74:66-86.

[30] Bartz B, Goldberg A. Medical Abortion. Clin Obstet and Gyn 2009; 52:140-50.

> clinical studies, including a 2004 Cochrane meta-analysis, reported that a regimen of 200 mg of oral mifepristone followed 24 to 48 hours later by 800 mcg of vaginal misoprostol results in complete abortion in 96% of cases at gestations of up to 63 days and that increasing the mifepristone dose to 600 mg does not improve efficacy."

In a 2010 review article covering 25 years of the clinical development of mifepristone followed by a prostaglandin for MAB, Spitz[31] noted similar conclusions:

> "In the US, most investigators administer 200 mg rather than 600 mg mifepristone as many trials have shown equivalent results with these two dose schedules. A recent meta-analysis of four randomized controlled trials compared the two dose regimens. Endpoints were complete abortion, continuing pregnancy and side effects. The two doses *[600 v. 200 mg mifepristone]* result in similar rates of complete abortion with no difference in adverse events."

Another change in clinical practice was related to the labeling stipulation that women return to the clinic/office two days after Mifeprex was administered to take the misoprostol dose. Many experts involved with termination of early pregnancies also advocated misoprostol self-administration at home to mitigate the time, travel and inconvenience of this additional visit.

In the US, the American College of Obstetricians and Gynecologists (ACOG), National Abortion Federation[32], and PPFA currently all endorse the lower oral dose of mifepristone followed in 24-48 hours with misoprostol. According to the 2014 ACOG Practice Bulletin, the misoprostol route of administration may be oral, buccal, sublingual or vaginal; sublingual administration, however, has a more rapid absorption resulting in a higher incidence of adverse side effects.[1]

<u>European practice</u>:

In December 2011, the International Federation of Obstetrics and Gynaecology (FIGO) published revised guidelines for the use of mifepristone and misoprostol for MAB up to 63 days, 64-84 days, and after 84 days (12 weeks) gestation.[33] The FIGO recommended regimens using 200 mg of oral mifepristone followed by 800 mcg of misoprostol administered vaginally, buccally, or sublingually. Up to 57-63 days gestational age, misoprostol is taken 24-48 hours after mifepristone. Per the review of data available to them, FIGO decided additional doses of 400 mcg misoprostol may be

[31] Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. Contraception 2010;82:442–52.

[32] National Abortion Federation Guidelines 2015.

[33] Faundes A. The combination of mifepristone and misoprostol for the termination of pregnancy. *Int J Gynecol Obstet* 2011;115:1-4.

safely used depending on gestational age, and these combinations result in a complete termination in more than 95% of cases.

Similar guidelines using either vaginal, buccal, or sublingual misoprostol are endorsed by the World Health Organization (WHO), the United Kingdom Royal College of Obstetricians and Gynecologists[34], and a recent Cochrane Review (2011, Issue11).[35]

Reviewer's Comment:

From the above discussion, it is clear that the standard of care in the US for early MAB has deviated from the FDA-approved dosing regimen. PPFA provides the largest number of medical abortions each year in the US and as early as 2001, was already using the regimen of 200 mg oral mifepristone followed 24-48 hours later by 800 mcg vaginal misoprostol.

There are a large number of studies and reviews that support the efficacy of the proposed new dose regimen through 63-70 days gestation. Efficacy was defined in these studies as a complete expulsion of the pregnancy without need for surgical intervention for any reason during the follow up period. The 2015 review by Chen and Creinin summarized clinical outcomes and adverse effects from 20 MAB studies including a total of 33,846 women using regimens consisting of 200 mg oral mifepristone followed by buccal misoprostol through 70 days gestation. All studies except two used 800 mcg misoprostol. Two studies (827 women) used 400 mcg buccal misoprostol. Six studies used a 24-hour time interval between mifepristone and buccal misoprostol administration and 14 used a 24-48 hour window for the dosing interval. The table below lists the 15 studies using the proposed doses (200 mg plus 800 mcg) with a 24-48 hour dosing interval.

[34] Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline Number 7. 3rd ed. London (UK):RCOG Press 2011.

[35] Kulier R, Kapp N, et al. Medical methods for first trimester abortion (Review). The Cochrane Library 2011, Issue 11:1-126.

Table 3: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later - US Studies

Study &Year	Design, Location	Gestation (maximum days)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Middleton 2005[24] US	**Prospective**	56	24-48	216	94.9
Winikoff 2008[23] US	**Prospective**	63	24-36	421	96.2
Fjerstad 2009[27] US	**Retrospective**	59	24-48	1,349	98.3
Grossman 2011[36] US - Clinic Mife v. Tele-med	**Prospective**	63	24-48	449	Clinic: 96.9% Telemed: 98.7%
Winikoff 2012[19] US	**Prospective**	57-70	24-48	629	93.2
Gatter 2015[13] US	**Retrospective**	63	24-48	13,373	97.7
Chong 2015[17] US	**Prospective**	63	24-48	357	96.7
TOTALS	**7 Studies**	**56-70 days**	**24-48 hr**	**16,794**	**97.4**

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

[36] Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.

Table 4: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later- Non- US Studies

Study &Year/Country	Design, Location	Gestation (maximum)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Alam 2013[37] Bangladesh	**Prospective**	63	24	629	92.7
Blum 2012[70]	**Prospective**	63	24	210	92.9
Boersma 2011[22] Curacao	**Prospective**	70	24-48	307	97.7
Chai 2013[38] Hong Kong	**Prospective**	63	48	45	95.6
Dahiya 2012[39] India	**Prospective**	50	24	50	92
Chong 2012[40] Georgia, Vietnam	**Prospective**	63	36-48	560	96.4
Giri 2011[41] Nepal	**Prospective**	63	24	95	93.6
Goldstone 2012[20] Australia	**Retrospective**	63	24-48	11,155	96.5
Louie 2014[14] Azerbaijan	**Prospective**	63	24-48	863	97.3
Ngo 2012[42] China	**Retrospective**	63	36-48	167	91.0
Ngoc 2011[43] Vietnam	**Prospective**	63	24	201	96.5
Ngoc 2014[16] Vietnam	**Prospective**	63	24-48	1,371	94.7
Olavarietta 2015[85] Mexico	**Prospective**	70	24	884	98.2
Pena 2014[44] Mexico	**Prospective**	70	24-48	971	97.3

[37] Alam A, Bracken H et al. Acceptability and Feasibility of Mifepristone-Misoprostol for Menstrual Regulation in Bangladesh. Intnational Persp on Sexual and Reprod Health 2013;39(2):79-87.

[38] Chai J, Wong CY, Ho PC. A randomized clinical trial comparing the short-term side effects of sublingual and buccal routes of misoprostol administration for medical abortions up to 63 days' gestation. Contraception 2013;87:480-5.

[39] Dahiya K, Ahuja K, Dhingra A et al. Efficacy and safety of mifepristone and buccal misoprostol versus buccal misoprostol alone for medical abortion. Arch Gynecol Obstet 2012; 285: 1055-8

[40] Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. Contraception 2012;86:251-6.

[41] Giri A, Tuladhar H et al. Prospective study of medical abortion in Nepal Medical College- a one year experience. Nepal Medical Coll J 2011;13(3):213-15.

[42] Ngo TD, Park MH, Xiao Y. Comparing the WHO versus China recommended protocol for first trimester medical abortion: a retrospective analysis. Int J Womens Health 2012;4:123-7.

[43] Ngoc NTN, et al. Comparing two early medical abortion regimens: mifepristone+misoprostol vs. misoprostol alone. Contraception 2011;83:410-17.

[44] Pena M, Dzuba IG, Smith PS, et al. Efficacy and acceptability of a mifepristone-misoprostol combined

Sanhueza 2015[48] Mexico	**Prospective**	70	24-48	896	93.3
TOTALS	**15 Studies**	**56-70 days**	**24-48 hrs**	**18,425**	**96.1%**

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

Reviewer's comments:

The data above in Table 3 and Table 4 from ~16,800 US women and ~18,400 non-US women in clinical studies of MAB through 70 days gestation with success rates of 97.4% (US) and 96.1% (non-US) strongly support the proposed new dosing regimen and the extension of the acceptable gestational age. The number of US and non-US studies, the number of evaluable women, and the overall complete abortion rates (termination with no surgical intervention) will be described in the efficacy table in Section 14 CLINICAL STUDIES in the new approved label. Additional discussion on increasing the gestational age through 70 days follows in the next major section.

Precise timing of the administration of misoprostol has not been shown to result in a higher success rate which is why the majority of the above studies allowed a range of hours between the mifepristone dose and misoprostol dose rather than one set time between the two drugs. The 2013 Raymond systematic review[18] of 87 studies that exclusively used a mifepristone 200 mg oral dose in over 45,000 women, followed by varying doses and routes of administration of misoprostol, concluded that if the mifepristone-misoprostol interval is < 24 hours, the procedure is less effective compared to an interval of 24-48 hours.

Another study[45] also looked at the question of the mifepristone-misoprostol interval. The authors conducted a systematic review of randomized controlled trials published from 1999 to 2008 to assess the evidence for a shorter mifepristone and misoprostol administration interval for first trimester medical termination. Searching strategy included MEDLINE, EMBASE, CLINAHL and Cochrane Library. The primary outcome measure was complete abortion without the need for a surgical procedure. "Five randomized controlled trials (RCTs) compared the efficacy of mifepristone-misoprostol administration intervals between 0 and 72 hours in 5,139 participants. The complete abortion rates varied between 90% and 98%. Although the meta-analysis of pooled data of all five RCTs showed no statistically significant difference in efficacy between

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regimen for early induced abortion among women in Mexico City. Int J Gynaecol Obstet 2014;127:82-5.

[45] Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. Contraception 2010;81(4):269-74. doi: 10.1016/ j.contraception.2009.09.007. Epub Oct 29, 2009.

the shorter and longer dosing intervals, there was a trend toward slightly lower success rates with administration intervals < 8 hours." This study supports the finding that the proposed regimen is effective with the 24-48 hour flexible interval. Labeling will indicate that the regimen may not work as well if the misoprostol is taken earlier than 24 hours after Mifeprex.

Reviewer's Final Recommendation:

The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol should be approved; there are sufficient data from the medical literature with over 35,000 women supporting the regimen's efficacy (termination without any additional surgical intervention) as being in the 91-98% range.

6.1.7 Increase in gestational age from 49 days to 70 days

Original NDA review:

The US clinical trial[31] was conducted from September 1994 to September 1995 and treated 2,121 women. A total of 2,015 women (95%) returned at the 14-day follow-up visit. The trial categorized women into three groups based on gestational age at the time of procedure, and evaluated the rates of "Success" (a complete pregnancy termination without use of any additional doses of misoprostol or surgical intervention), and the rates of "Failure" (with four sub-categories of incomplete abortion, ongoing pregnancy, intervention for medical reason, and intervention solely because of patient request). The success and failure data are shown in Table 5.

Table 5: Original NDA Efficacy Results

OUTCOME	≤ 49 Days N= 827 (%)	50-56 Days N= 678 (%)	57-63 Days N= 510 (%)
Success (mifepristone + misoprostol	**762 (92)**	**563 (83)**	**395 (77)*†**
Failure (any surgical intervention for any reason) N (%)			
Total failures	**8%**	**17%**	**23%*†**
Incomplete abortion	39 (5)	51 (8)‡	36 (7)
Ongoing pregnancy	8 (1)	25 (4)*	46 (9)* §
Medical indication for intervention	13 (2)	26 (4)‡	21 (4)‡
Patient's request for intervention	5 (0.6)	13 (2)	12 (2)‡

***P<0.001 for the comparison with the ≤ 49-days group.**

†P= 0.02 for the comparison with the 50 to 56-days group.

‡ 0.001 ≤ P<0.03 for the comparison with the ≤ 49-days group.

§ P<0.001 for the comparison with the 50 to 56-days group.

Source: Modified from Table 1, pg 1243 in the Spitz NEJM article (1998).

Reviewer's comments:

Looking at the results in the table above, it is reasonable that the approved use was only for women in the first 49 days' gestation, given the 8% "failure rate" in this subgroup, compared to 17% and 23% failure rates for the longer gestations. It is important to note that failure was defined as any case requiring surgical intervention for any of the following reasons:

- **incomplete abortion (incomplete expulsion)**
- **documented ongoing pregnancy**
- **medical reasons (usually heavy vaginal bleeding with or without retained products of conception)**
- **patient request (usually for bleeding)**

As has been pointed out, since the US trial data used for the FDA approval of Mifeprex, given the experience and data gained in the last 20 years from millions of women in the US and abroad, the success rates and overall outcomes are very different. Currently, when a "failure" occurs, using the original definition, options that are now commonly available include the following:

- **expectant management (wait and see) in the case of an incomplete abortion (i.e., pregnancy terminated but not fully expelled)***
- **medical treatment for bleeding, pain and other common symptoms**
- **clinical evaluation with the use of 1) office ultrasound and/or 2) hCG data determined by rapid, sensitive urine and/or serum testing***
- **additional doses of misoprostol for an incomplete abortion***
- **less invasive surgical intervention (vacuum aspiration) in the clinic/office instead of a D&C under anesthesia in an operating room**
- **continuing the pregnancy (although the medical recommendation is to proceed to a surgical abortion in such a case, we acknowledge that a woman could potentially decide to continue the pregnancy)**

*** per protocol, these options were NOT available in the original US trial**

It is also evident that the proposed new dosing regimen is considerably more effective for all gestations through 70 days [see data and discussion that follows for 57-63 and 64-70 days gestation], especially when compared to the original data using the FDA-approved regimen which had "success" rates of only 83% and 77% at 50-56 and 57-63 days gestation, respectively.

Current evidence for increasing the gestational age to 70 days

Current evidence demonstrates that the new proposed medical abortion regimen is effective for women in the range of 57-63 days and 64-70 days of gestation. A 2015

systematic review identified six published studies that recorded data on outcomes of medical abortions performed during gestational Days 64-70.[46]

The published studies were conducted in the United States, UK, Mexico, Curaçao, Vietnam, and the Republic of Georgia. All subjects were treated as outpatients between 2007 and 2015. The older UK study evaluated 127 women who were at 64-70 days gestation and treated with 200 mg oral mifepristone followed by 800 mcg vaginal misoprostol.[47]

Reviewer comment:

We evaluated the data separately for 57-63 and 64-70 days of gestation. The following two tables show the efficacy data for 57-63 and 64-70 days gestation (also known as Week 9 and Week 10).

[46] Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70days gestation. Contraception 2015;92:197-9.

[47] Gouk EV, et al. Medical termination of pregnancy at 63-83 days gestation. British J Obstet Gyn 1999;106:535-539.

Table 6: MAB Efficacy Outcome 57-63 Days Gestation

Study	Enrolled N	Followed N	Success N (%)	Ongoing Pregnancy N (%)	Lost to Follow up %	Comment
Winikoff [23] 2008 US-	132	115	109 (94.8)	2 (1.7)	13.0%	* Proposed Dosing
Winikoff [19] 2012 US	379	325	304 (93.5)	10 (3.1)	14.2%	* Proposed Dosing
Gatter[13] 2015 US	1527	1286	1228 (95.5)	21 (1.6)	15.8%	* Proposed Dosing
Sanhueza[48] 2015 Mexico City	196	190	171 (90.0)	6 (3.2)	3.1%	* Proposed dosing
Boersma[22] 2011** Curacao	105	95	91 (95.8)	2 (2.1)	9.5%	*Proposed dosing @ 24-36 hr @ home
Pena[44] 2014 Mexico City	177	171	164 (95.9)	2 (1.2)	3.4%	* Proposed dosing
Chong[40] 2012 Viet Nam, Georgia	86	85	79 (92.9)	2 (2.4)	1.2%	*Proposed dosing 36-48 hr
	81	81	77 (95.1)	2 (2.5)	0%	400 mcg buccal @ 36-48 hr
Bracken[49] 2014 4 countries-	389	382	362 (94.8)	7 (1.8)	1.3% (2 women withdrew)	400 mcg sublingual @ 24-48 hr
TOTAL	3,072	2,730	2,585 (94.7)	54 (2.0%)	11.1%	

***Mifepristone oral 200 mg followed in 24-48 hour range with misoprostol buccal 800 mcg.**

****Boersma study reported the interval from 50-63 days without further breakdown.**

Source: Data from published studies.

[48] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015;22:75-82.

[49] Bracken H ,Dabash R, Tsertsvadze G et al. A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial. Contraception 2014;89(3):181-6.

Reviewer comments:

Although the Chong and Bracken studies do not use the exact proposed dosing regimen, it is felt that their efficacy results are relevant because both used a lower dose of misoprostol, which, if anything, would have been expected to provide lower efficacy.

After careful review of the above eight studies, we find the following results. A combined total of 3,072 women were treated at 57-63 days of gestation, with 2,730 (88.9%) providing outcome data. Of these women, 2,585 (94.7%) had a complete medical abortion (pregnancy termination without any surgical intervention), and 54 (2.0%) had ongoing pregnancies. This successful treatment rate is better (94.7% compared to 92.1%) than the rate in the data on which the 2000 FDA Mifeprex approval was based. The data are sufficient and acceptable for extending the approval of Mifeprex up to at least 63 days gestation.

The numbers here do not exactly match the results shown in the efficacy table for 57-63 gestational days that are in Section 14 CLINICAL STUDIES in the new approved label, which is limited to studies using the identical dosing regimen to that proposed in this supplement. The number of evaluable women here is higher because the Chong and Bracken data are included, as noted above in the comment. The label, however, states the same conclusion of a 94.7% complete medical abortion rate and a 2% ongoing pregnancy rate.

Data for 64-70 days gestation are found in the next table.

Table 7: MAB Efficacy Outcome 64-70 Days Gestation

Study	Enrolled N	Followed N	Success N (%)	Ongoing Pregnancy N (%)	Lost to Follow up %	Comment
Winikoff[19] 2012	350	304	282 (92.8)	9 (3.0)	13.1	*Proposed dosing
Sanhueza[48] 2015	150	147	134 (91.2)	5 (3.4)	2.0	* Proposed dosing
Boersma[22] 2011†	26	26	25 (96.2)	1 (3.8)	0	Proposed dosing @ 24-36 hr @ home
Pena[44] 2014	2	2	2 (100)	0 (0)	0	* Proposed dosing
Chong[40] 2012 RCT	1	1	1 (100)	0 (0)	0	* Proposed dosing @ 36-48 hr
	6	6	6 (100)	0 (0)	0	400 mcg buccal
[Y]Gouk[47] 1999 UK-misoprostol in hospital	127	127	120 (94.5)	7 (5.5)	0	800 mcg vaginal @ 36-48 hr
Bracken[49] 2014	325	321	295 (91.9)	7 (2.2)	1.2	400 mcg sublingual @ 24-48 hr
TOTAL	987	934	865 (92.6)	29/934 (3.1)	53/987 (5.4)	

*Mifepristone oral 200 mg followed in 24-48 hour range with misoprostol buccal 800 mcg.

[Y]The Gouk study in 1996-97 included 253 women at 63-83 days gestation (Weeks 10-12).

Source: Table modified with data from published studies. See Abbas D et al. Contraception [MAB through 70 days gestation] 92 (2015):197-199.

Reviewer comments:

Use of the Chong and Bracken data is discussed above. Although the Gouk regimen used a different route of administration for misoprostol, the effectiveness of the vaginal route appears to be similar to that of the buccal route; therefore, these data are considered relevant. Data on sublingual administration of misoprostol may be less generalizable due to the different pharmacokinetic (PK) profile and higher AE frequency compared to buccal

administration. Also, see Section 4.4.3 Pharmacokinetics and the Cross Discipline Team Leader review.

The abortion success rates shown above from seven studies are comparable to (and in several studies, greater than) the success rates for medical abortion in the initial 2000 decision for Mifeprex up to 49 days gestation. The proportion of subjects with complete success without any medical or surgical intervention in the US pivotal trial that supported the original approval was 92.1%, as shown in Table 5, in 827 women encompassing all gestational weeks up to 49 days. The data in the above two tables include 3,072 women treated at 57-63 days gestation and 987 women at 64-70 days gestation. We believe that this comprises a sufficient number of women in each gestational week upon which to make a clinical decision, and that the overall 94.7% and 92.6% success rates are acceptable for approval.

The data here clearly establish the efficacy of medical abortion with mifepristone and misoprostol through 70 days gestation. At least two Gynuity Health studies of outpatient medical abortion through 70 days are ongoing, so more information from clinical studies will be available in the future.

It is also worth noting that in November 2015, the National Medical Committee of PPFA approved medical abortion through 70 days, so this is currently their standard of care.

Reviewer's Final Recommendation:

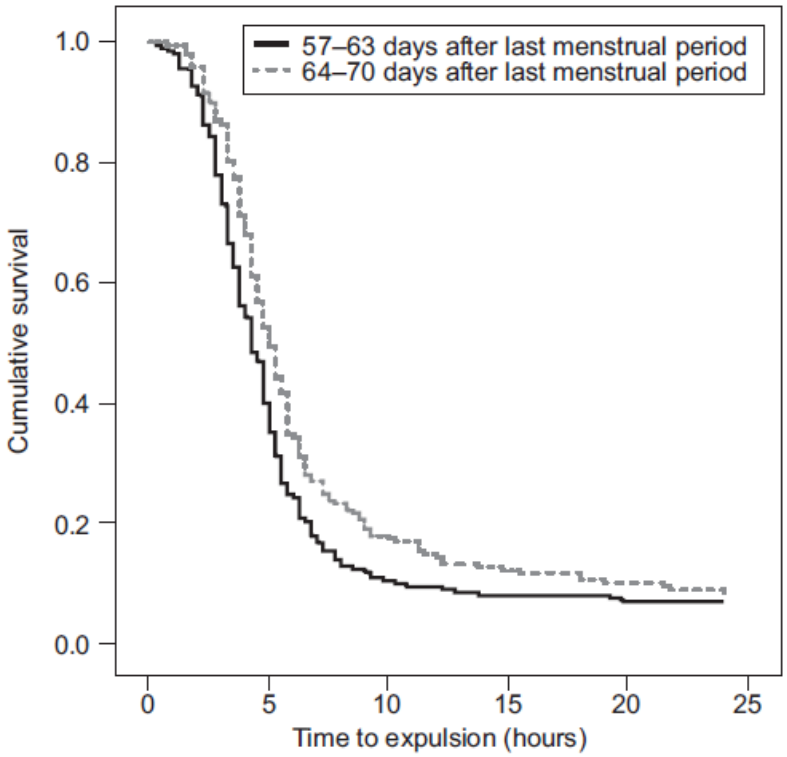
The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol should be approved for use through 70 days gestation (10 weeks from the first day of the LMP).

6.1.8 At-home Administration of Misoprostol

For the majority of women, the most significant cramping and bleeding will occur within 2-24 hours after taking misoprostol. Requiring women to take misoprostol in the office necessitates another visit and can interfere with the woman's ability to make reasonable plans for the expected bleeding and cramping. With the option to take misoprostol at home the woman can:

- **Plan to experience cramping and bleeding at a safe and convenient time when support is available**
- **Minimize loss of income (for childcare or missed days of work)**
- **Experience improved comfort, satisfaction and privacy**

Data (graph below) from Winikoff (2012)[19] shows the time in hours to complete expulsion of the pregnancy after misoprostol administration for gestations at 57-63 and 64-70 days. Within about 5 hours after misoprostol dosing, 50-60% of the MABs are complete.



Many studies have recorded data on home use in the US and elsewhere and "demonstrated that 87-97% of women find home use of misoprostol acceptable. Home use of misoprostol is now standard in the US."[50] The 2009-10 Swica comparative study focused on the option to take both mifepristone and misoprostol at home after being counseled at the office/clinic. There was no significant difference in either efficacy or safety for the 139 women (46%) who took both medications at home compared to 161 women who took mifepristone in the office and misoprostol at home.

Table 8 that follows is a list of studies where data are available on home use of misoprostol and the specific efficacy findings.

[50] Swica Y, et al. Acceptability of home use of mifepristone for medical abortion. Contraception 2013;88:122-127.

Table 8: Misoprostol Self-administration at Home

Study	Evaluable N	Misoprostol at home	Success	Comment
US Studies				
Gatter 2015[13] US	**13,373**	**All subjects** at 24-48 hr	97.7%	Through 63 days; buccal miso 800 mcg
Winikoff 2008[23] US	421	**All subjects** at 24-36 hr	96.2%	Through 63 days; buccal miso 800 mcg
Winikoff 2012[19] US	629	**All subjects** at 24-48 hr	93.5% (Wk 9) 92.8% (Wk 10)	**Week 9 v Week 10;** buccal miso 800 mcg
Swica 2013[50] US	301	**All subjects** at 6-48 hr	96.7 %- home mife 95.6%- clinic mife	Through 63 days; 800 mcg miso
Foreign Studies				
Louie 2014[14] Azerbaijan	863	794 (92%) at home at 24-48 hr	97%	Through 63 days; buccal miso 800 mcg
Pena 2014[44] Mexico	**1,000**	**All subjects** at 24-48 hr	97.3%	Through 63 days; buccal miso 800 mcg
Bracken 2014[49] 4 countries	703 (382 v 321)	543 (**77%**) took miso at 24-48 hr	94.8% (Wk 9) v 91.9% (Wk 10)	**Week* 9 v Week 10** 400 mcg sublingual miso used
Boersma 2011[22] Curacao	307	**All subjects** at 24-36 hr	97.7%	Through **70 days (Wk 10);** **GP care**; buccal miso 800 mcg;
Chong 2012[40] 400 v 800 buccal	1115 (559 v 563 were enrolled)	851 **(76%)** at 36-48 hr	96.8% with home miso; 95.1% with clinic miso	Through 63 days; ***DB, RCT in Vietnam and Georgia
Goldstone 2012[20] Australia:	**11,155**	**All subjects** at 24-48 hr	96.5%	Through 63 days; **buccal miso 800 mcg**
Sanhueza 2015[48]	**896**	**All subjects** at 24-48 hr	93.3	**Through 70 days (Wk 10)**
TOTAL	**30,763**	**30,210 (98.2%)**	**92%-97.7%**	**Different gestations, and regimens**

***DB, RCT: double-blind, randomized clinical trial.**

Source: FDA clinical reviewer table.

Reviewer comments:

The above table with data for home administration of misoprostol for 30,763 women in the US and other countries shows a success rate ranging from 91.9 to

97.7%. The two largest studies (Gatter and Goldstone) pooled showed 97% success using the new proposed dosing regimen with home use of buccal misoprostol. The lowest success rate above of 91.9% in the Bracken study is still supportive for approval and does not differ significantly from results with misoprostol taken in the clinic/office.

Of note is that 4 of the above studies provided data on home use of misoprostol through 70 days gestation.

Home use of misoprostol has been evaluated as part of the proposed protocol in studies including well over 30,000 patients, as well as in studies of home use of both mifepristone and misoprostol. The Raymond (2013) review[18] of early MAB with mifepristone 200 mg and misoprostol (different doses and routes of administration), analyzed 87 trials with 47,283 treated women up to 63 days gestation. The article concludes: "We found no evidence that allowing women to take the misoprostol at home increased the rate of abortion failure or serious complications." It is also notable that the NAF and ACOG guidances encourage home administration of misoprostol and it has been standard protocol for most PPFA clinics for since 2005.

While we do not have age-specific efficacy data for adolescents who took misoprostol at home, it is evident that many adolescents did take buccal misoprostol at home. In the Goldstone 2012 study, there were eight 14 year olds and 931 women ages 15-19 who took misoprostol at home. In the Gatter 2015 study, there were 24 adolescents age 11-14, 82 age 15, 216 age 16, and 435 age 17 who took misoprostol at home. The overall efficacy in these two large studies was excellent, as previously noted.

Reviewer's Final Recommendation:

There is no medical rationale against permitting the woman to be given the misoprostol on the day of the initial clinic/office visit and self-administer it at a convenient time in the next 24-48 hours at home. This would avoid another visit and the time, transportation, loss of work, inconvenience, etc. that such a visit would involve. Furthermore, given the fact that 22-38% of women abort within 3 hours and 50-60% within 5 hours of buccal misoprostol[19], it is preferable for the woman to be in a convenient, safe place (home or at a support person's location) for the expected uterine cramping and vaginal bleeding to occur. The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol shows acceptable efficacy when misoprostol is self-administered at home.

6.1.9 Use of a Repeat Dose of Misoprostol if Needed

Several studies using buccal misoprostol allowed the option of repeat misoprostol at follow-up one week after mifepristone for persistent gestational sac; however, only a few

studies report specific outcomes. The Chen and Creinin 2015 review[12] of mifepristone with buccal misoprostol for MAB reported on four studies. Chong (2012)[40] provided additional information from 1,122 women. In the study protocols, women with an ongoing pregnancy at follow-up were recommended to undergo uterine suction curettage, whereas women who had retained products of conception were given the options of expectant management, suction curettage/aspiration, or a second dose of misoprostol. Limited additional data were provided by Gatter (2015)[13]: data on the use of a repeat dose of misoprostol were available from a subset of 7,335 women, of whom 87 (1.2%) received a repeat dose. Efficacy results, however, are not stated in the Gatter article, so this study is not included in Table 9, which highlights success rates after a repeat dose of misoprostol in seven published articles that included this specific outcome.

Table 9: Success with a Repeat Dose of Misoprostol - Incomplete MAB

Study/Country	Total N	Mife-Miso Interval (hrs)	Took 2nd Dose	Success with 2nd dose N (%)	Comment
***Raghavan 2010[51] Moldova**	277	24	2	2 (100)	Buccal Miso 400
***Winikoff 2008[23] US**	421	24-36	14	13 (93)	Buccal Miso 800
***Winikoff 2012[19] US**	629	24-48	[Y]20	[Y]Wk 9- 11 (91) Wk 10: 9 (67)	Week 9 v. Week 10: Buccal Miso 800
***Louie 2014[14] Azerbaijan**	863	24-48	16	16 (100)	Buccal Miso 800
Chong 2012[40] Georgia, Vietnam	1122	36-48	47	43 (92)	Buccal Miso 400 and 800 mcg
Boersma 2011[22] Curacao	307	24-36 hr	5	4 (80)	GP care; Buccal Miso 800 at home
Bracken 2014[49] 4 countries	703	24-48 hr	33	29 (88)	Sublingual Miso 400
TOTALS	**4,018**	**--**	**137 (3.4%)**	**123 (90%)**	

***These 4 studies are in Table 4 of the Chen and Creinin 2015 review article.**

[Y]These data are directly from the Winikoff article; the Chen and Creinin review had incorrect data.

Source: table modified by FDA reviewer from Chen and Creinin 2015 article and 3 other studies.

[51] Raghavan S, et al. Comparison of 400 mcg buccal and 400 mcg sublingual misoprostol after mifepristone medical abortion through 63 days' LMP: a randomized controlled trial. Contraception 2010; 82:513-9.

Reviewer's comment:

The completion success rates shown above are high. While only 3.4% of the women took a second misoprostol dose, 90% of these women avoided a surgical procedure to complete their termination. We believe the option of a repeat dose of misoprostol is acceptable and safe in the case that complete expulsion has not occurred after initial dosing (provided that the pregnancy is not still ongoing): it offers a choice for the healthcare provider and the patient on how to manage an incomplete expulsion (retained products of conception) following the initial treatment. As noted above, the other options are expectant management, suction aspiration in the office, or a surgical D&C in the operating room. It is also of note that it is standard protocol in many US clinics to offer the choice of a repeat misoprostol dose, especially for women with an incomplete termination (retained tissue/clots or a documented non-viable pregnancy). A second dose of misoprostol is generally not offered in the case of a documented ongoing pregnancy following use of mifepristone and misoprostol.

Reviewer's Final Recommendation:

Use of a repeat dose of misoprostol may be offered when using the new dosing regimen if the pregnancy has ended, but the expulsion is incomplete.

6.1.10 Physician v Other Healthcare Provider Treatment

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies took place in varying settings (urban, rural, international, low resource). The efficacy results are as follows:

- Olavarietta[85] demonstrated efficacy of 97.9% when the MAB was provided by nurses as compared with 98.4% with physicians
- Kopp Kallner[84] showed efficacy of 99% with certified nurse midwives versus 97.4% with physicians
- Warriner[52] demonstrated efficacy of 97.4% with nurses versus 96.3% with physicians
- Puri[83] showed efficacy of 96.8% compared with 97.4% in the "standard care" group

Reviewer comment:

The above findings for MAB efficacy from 5 studies clearly demonstrates that efficacy is the same with non-physician providers compared to physicians or the

[52] Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-61.

"standard care" treatment.

6.1.11 Follow-up Timing and Method

Concerning follow-up timing and method, follow-up within the 7-14 day interval after mifepristone administration is universally recommended; however, follow-up does not necessarily need to be done as currently labeled "in the clinic or healthcare provider's office 14 days after Mifeprex administration."

One strong argument for flexibility in follow-up timing, location and method after the administration of Mifeprex and misoprostol is to avoid placing an undue burden on either the provider or the patient, while maintaining the ability to identify incomplete terminations. The currently approved labeling specifies three visits (two for dosing, one for follow-up) at fairly rigid times that are often not practical, convenient or necessary.

Several articles were submitted by the Applicant to support flexible follow-up. The most noteworthy article is the 2013 Raymond review[18] of over 45,000 MABs using 200 mg oral mifepristone that concluded: "we observed no significant association between abortion failure rates and the timing of the follow-up evaluation." This topic is discussed thoroughly in the Section Submission-Specific Primary Safety Concerns.

Reviewer comment:

Follow-up during the 7-14 day window after the administration of mifepristone is necessary to determine that the termination was successful and the woman is in good health. If for some reason the follow-up contact is not made (the woman is "lost to follow-up"), the clinical guidelines of NAF state that "all attempts to contact the patient (phone calls and letters) must be documented in the patient's medical record." This guideline emphasizes the importance of follow-up but accepts the fact that women are sometimes lost to follow-up and there is no mechanism that can guarantee 100% follow-up in the normal clinical setting.

Reviewer's Final Recommendation:

Follow-up after taking Mifeprex and misoprostol is necessary. The exact timing and method should be flexible and determined jointly by the healthcare provider and the individual woman being treated, and should follow the standard guidelines for the office/clinic where the Mifeprex is being dispensed. Fortunately, there are several choices/methods of follow-up that can be used and it appears that no single option is superior to the others. The woman should always have the option to be seen at the office/clinic.

6.1.12 Subpopulations

Parity

The Raymond (2013) review article[18] had 74 trials with parity data for ~ 32,000 women. In 34 trials whose study populations comprised > 50% nulliparous women, the MAB success rate was 96.4%; in 40 trials with ≤ 50% nulliparous women, the success rate was 94.9%. This suggests that women who have not had a previous term pregnancy

delivery have a slightly higher early MAB success rate. These data are not definitive, however, because such factors as the dosing regimen, route of administration, and gestational age could also influence the success rates.

Previous abortion

One study[26] found that success rates are slightly better in women who have not had a previous abortion. Prior abortion, however, did not appear to be an important risk factor for abortion failure or success (Raymond[18].

Race

There does not appear to be any efficacy difference based on race. Results are reported in studies enrolling a large number of women. Gatter (2015)[13] had five racial/ethnicity groups among over 13,000 women at the PPFA centers in the Los Angeles area; the success rates ranged from a low of 97.2% (African-American) to a high of 97.8% (White, Asian and Other), which is not clinically or statistically significant.

Adolescents v. Older Women

There are at least three articles that support the efficacy of MAB in adolescents; each study used the same definition of success as the need for no further medical or surgical intervention:

- Phelps et al. 2001[53] conducted a pilot study in 28 adolescents aged 14-17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. All 28 had complete medical terminations without complications or surgical intervention. Five adolescents did not require any misoprostol.
- Niinimaki et al. April 2011:[54] Finnish Registry from 2000-06 comparing rates of AEs in adolescents and adult women with MAB at ≤ 20 weeks gestation, which included 3,024 women < age 18 and 24,006 women age 18 or older. By gestational age, 2,424 adolescents were < 64 days gestation and 139 were within 64-84 days gestation. The specific dose regimens are not stated and may have varied according to the gestational ages. The odds ratio for an incomplete abortion for adolescents under age 18 compared to the women ≥ age 18 was 0.69, meaning that the younger women had a lower rate of incomplete abortions.
- Gatter, Cleland and Nucatola (2015):[13] US data using the proposed regimen of mifepristone 200 mg and misoprostol 800 mcg buccally through 63 days included 283 women aged 17 years and 322 under age 17 (see Table 10). The 605 women under age 18 had a 98.7% success rate while the 6,674 18-24 year olds had a 98.1% success rate. The four older age groups had success rates that ranged from 96.5 to 97.5% without any need for a surgical procedure and additional treatment. In

[53] Phelps RH, et al. Mifepristone abortion in minors. Contraception 2001;64:339-343.

[54] Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

the pediatric population, there were no cases requiring transfusion, hospitalization or treatment for severe infection.

The table below shows the age distribution from the Gatter study. There were 24 adolescents between ages 11-14, 82 adolescents age 15, and 216 age 16 totaling 322 adolescents. As noted, 283 adolescents were age 17.

Table 10: MAB Success by Age Group

Age Group (years)	Total N Success (%)	Comment
< 18	**605 (98.7)**	**322 were age 11-16 283 were age 17**
18-24	6684 (98.1)	The age distribution here is representative of other US data on MAB - largest group is age 18-24 followed by age 25-29
25-29	3317 (97.5)	
30-34	1613 (96.5)	
35-39	855 (97.0)	
40+	299 (97.3)	
TOTAL	**13,373 97.7% overall success**	

Source: Data from Gatter 2015 review.

Reviewer comments:

Data from 3,657 adolescents under age 18 in the above three studies shows a MAB success rate that is consistently equal to or higher than that found in the women older than age 17. It is interesting that five (18%) of the adolescents in the Phelps study did not even need misoprostol. The percentage of women not needing any misoprostol is generally much lower, perhaps 1-3%, in other early MAB studies. From the articles reviewed, efficacy of early MAB in the adolescent population is not a concern.

Additional adolescent data were reported in the Goldstone 2012 study[20], where there were eight 14 year olds and 931 women ages 15-19 who took misoprostol at home for a MAB up to 63 days gestation. Efficacy and safety data by age groups were not reported in the article.

6.1.13 Analysis of Clinical Information Relevant to Dosing Recommendations

As noted in some of the reviewer comments and tables, there is evidence that lower doses of misoprostol (400 mcg), other ROAs (vaginal and sublingual), inclusion of more advanced gestational ages, and different dosing intervals between mifepristone and misoprostol have shown acceptable efficacy and safety results. However, for the purposes of this NDA review, our final recommendations are focused on the dosing regimen and other requests specifically made by the Applicant.

6.1.14 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. Return to fertility is well-documented: in the Patient Counseling Information section, the labeling states "inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses" and "inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before she resumes sexual intercourse."

6.1.15 Additional Efficacy Issues/Analyses

The Applicant has requested that revised labeling provide only for the new proposed regimen and that the original approved regimen be deleted.

Reviewer Final Recommendation:

While there are no safety or efficacy reasons that would lead us to withdraw approval of the currently labeled dosing regimen, we concur that it may be deleted from labeling because very few providers currently use it, and inclusion of two options for dosing could be confusing. Of note, PPFA and NAF guidelines have used mifepristone 200 mg oral and misoprostol 800 mcg (initially given vaginally and now buccally) since 2001.

7 Review of Safety

Safety Summary

- Medical abortion with the new proposed regimen of Mifeprex 200 mg followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation is safe. Major adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are reported rarely in the literature on over 30,000 patients. The rates, when noted, are exceedingly rare, generally far below 0.1% for any individual adverse event. The number of postmarketing deaths associated with Mifeprex pharmacovigilance is very low. Non-vaginal routes of administration of misoprostol have increased and since the *C. sordellii* deaths associated with vaginal misoprostol, there have been no *C. sordellii* deaths. Given that the numbers of these adverse events appear to be stable or decreased over time, it is likely that these serious adverse events will remain acceptably low.

- Common adverse events associated with medical abortion occur at varying but acceptable rates.

- There are scarce cases of uterine rupture associated with early medical abortion. Medical abortion using mifepristone with or without misoprostol in the first trimester is safe from this perspective.

- There does appear to be an association between angioedema and mifepristone administration. The risks of anaphylaxis and angioedema should be included in the labeling for Mifeprex and there should be continued pharmacovigilance for anaphylaxis.

- Home use of misoprostol has been evaluated as part of the proposed dosing regimen in studies including well over 30,000 patients, demonstrating an acceptable safety profile, with rates of adverse events equal to or lower than those with the approved regimen requiring in-office dispensing of misoprostol. Home use of misoprostol can increase patient convenience, autonomy and privacy without increased burden on the healthcare system.

- In the articles about repeat misoprostol after mifepristone administration, there is little information provided about safety. The need for a second dose is a relatively uncommon occurrence. In studies of medical abortion using misoprostol alone, using two or more doses as compared to one dose of misoprostol does increase the risk of the common adverse event of diarrhea. There are a very few reports of uterine rupture with multiple doses of misoprostol, in almost all cases in women with prior uterine surgery, such as a cesarean section.

- The Applicant demonstrates that alternatives to in-clinic follow-up, including standardized questions, telephone follow-up, and use of low and high sensitivity urine pregnancy tests, serum pregnancy tests, and ultrasound are effective and safe. Loss-to-follow-up rates do not exceed those of in-clinic follow-up. This option can increase flexibility and accessibility of medical abortion for women.

- Medical abortion in adolescents appears to be at least as safe, if not safer, as in adult women. These data support the safety of Mifeprex in adolescents and satisfy requirements for PREA. No information on safety or efficacy if used in premenarchal girls is required, as the medication is not indicated in that subset of the pediatric population.

- Midlevel providers in the United States, such as nurse practitioners, nurse midwives and physician assistants currently provide family planning services and abortion care, including medical abortion care, under the supervision of physicians. In light of the REMS requirements, midlevel providers who are currently practicing abortion care are doing so under the supervision of physicians. Therefore, facilities that employ midlevel providers already have an infrastructure in place for consultation and referral if, as required under the REMS, a prescriber is unable to provide additional care, including surgical management if needed.

- It is appropriate to modify the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." FDA has received

such reports for 15 years, and it has determined that the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely. For this reason, FDA does not believe ongoing reporting of all of the specified adverse events is warranted. The proposed Prescriber's Agreement Form (to replace the Prescriber's Agreement) will continue to require that qualified healthcare providers report any deaths. The Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience.

- Upon review of historical documents and of current guidelines for REMS materials, the phrase "under Federal law" can be removed from the Prescribers' Agreement. We concur with (b) (6) review of the REMS document.

- The revised Indication Statement should read:

"Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation." Safe use of Mifeprex would be enhanced when other information necessary to describe appropriate use (i.e., the need to use Mifeprex in a combined regimen with misoprostol and the gestational age for use) is included in the Indication Statement. This would be consistent with current FDA thinking (e.g., the internal Label Review Tool) which states that the indication and use statement should include "Information if drug is to be used only in conjunction with another therapy."

7.1 Methods

The assessment of the clinical safety of Mifeprex through 70 days gestation is based on the Applicant's submission of numerous articles from the peer-reviewed medical literature. The various studies have different designs, inclusion criteria, dosing regimens and endpoints for safety and efficacy. For the evaluation of safety, this reviewer focused on the studies that evaluated the proposed dosing regimen . All the articles used for this review can be found in the extensive list of references in Section 9.6 at the end of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The reviewer evaluated safety based on the studies that focused on the proposed dosing regimen, specifically Mifeprex 200 mg followed by misoprostol 800 mcg buccally 24-48 hours later, as listed in Table 11 below. Supportive data from studies that have less specific numerical data or studies that included other regimens, specifically with different routes of administration of misoprostol (vaginal, oral, sublingual) are not included in this portion of the review, but are discussed in Sections Major Safety Results and Supportive Safety Results. Table 11 lists the studies referenced in these discussions.

Table 11: Studies Used to Evaluate Safety

Study	
USA	**International**
Gatter 2015[13], retrospective	Ngoc 2014[16], Vietnam, prospective
Ireland 2015[15], retrospective	Goldstone 2012[20], Australia, retrospective
Chong 2015[17], prospective single-arm	Boersma 2011[22], Curacao, prospective
Winikoff 2012[19], prospective	
Grossman 2011[36], prospective	
Winikoff 2008[23], prospective RCT	
Creinin 2007[25], prospective	
Middleton 2005[24], prospective	

Source: NDA clinical reviewer table.

7.1.2 Categorization of Adverse Events

For the purposes of this review, adverse events categorized as serious include death; hospitalization; infection, including severe infection requiring hospitalization; bleeding requiring transfusion; and ectopic pregnancy. Other non-serious adverse events include: nausea, vomiting, diarrhea, fever, bleeding and cramping.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The data are not pooled across studies as the study designs are quite different. The incidence of individual adverse events is noted for each study, and can be used to provide an estimated range.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Per the Applicant, there have been approximately 2.5 million US uses of Mifeprex by US women since its approval in 2000. If evaluation is limited to the studies listed in Table 11 focusing specifically on the proposed new dosing regimen, exposure for this safety analysis is based on well over 30,000 patients. The exact number cannot be determined because two retrospective studies (Gatter[13] and Ireland[15]) are likely based on overlapping cohorts of patients from Planned Parenthood clinics in Los Angeles. There are likely some differences in the demographic data for the different studies; therefore, the descriptions are separated into US and international data. However, it is doubtful

that demographic differences such as race or ethnicity are clinically meaningful in relation to the safety and efficacy of medical abortion. The data do include adolescents exposed to Mifeprex; information on safety in this population is discussed in Section 7.4.5.

7.2.2 Explorations for Dose Response

NA for this review.

7.2.3 Special Animal and/or In Vitro Testing

NA for this review.

7.2.4 Routine Clinical Testing

From this reviewer's assessment of the literature, no routine clinical testing is needed to evaluate the proposed changes to the Mifeprex labeling.

7.2.5 Metabolic, Clearance, and Interaction Workup

NA for this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please see Important Safety Issues with Consideration to Related Drugs for discussion of potential adverse events for drugs in this class.

7.3 Major Safety Results

7.3.1 Deaths

Deaths are rare with medical abortion. Most of the articles provided did not specifically report on deaths with medical abortion. Among the seven US studies, only one reported on deaths (Grossman, 2011[36]) and noted zero deaths among 578 subjects. Among the three international studies, only one[20] reported on deaths. In this retrospective review of 13,345 medical abortions with the proposed regimen, the authors reported only one death, yielding a rate of 0.007%. More information on deaths associated with medical abortion is found in Section 8 Postmarket Experience.

7.3.2 Nonfatal Serious Adverse Events

The nonfatal serious adverse events typically discussed in the literature are hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. See narratives below and Table 12, Table 13, and Table 14 for details.

Hospitalization data:

Most articles do not report hospitalization data. In the US studies, 19 patients were reported as being hospitalized out of a total of 16,696 subjects. The overall rates range

from 0.003-1.1%. Only three articles separated out hospitalizations by gestational age. In Gatter 2015[13], there were 3/8495 hospitalizations among women ≤ 49 days, 3/3142 among women at 50-56 days gestation and none among women at 57-63 days. In Winikoff 2012[19], there were only two hospitalizations, both among women at 57-63 days, and none in the 64-70 days gestation group. In Creinin[25] two of six total hospitalizations were in the 50-56 days group and two in the 57-63 days group. The two remaining hospitalizations in that study were unrelated to study drug and gestational age information was not provided for these two cases. There were none among women at 64-70 days gestation. See Table 12 below.

Among the international studies, only 3 of 15,109 women were hospitalized, with rates from 0.07-0.6%. These rates were not separated out by gestational age. See Table 12.

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Table 12: Hospitalizations by Gestational Age

Study	Design	Subjects (N)	Hospitalizations by gestational age [Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
USA							
Gatter 2015[13]	retrospective	13,373	6‡ (0.04%)	N=8945 3/8945 (0.03%)	N=3142 (0.1%)	N=1286 0	N/A
Chong 2015[17]	prospective	400	2 (0.5%)	NR*	NR	NR	N/A
Winikoff 2012[19]	prospective	729	2 (0.27%)	N/A	N/A	N=325 2 (0.61%)^	N= 304 0%
Grossman 2011[36]	prospective	578	0	N=283 0%	N=103 0%	N=63 0%	N/A
Winikoff 2008[23]	prospective	421	3(0.71%)	N=213 NR	N=93 NR	N= 115 NR	N/A
Creinin 2007[25]	prospective	546	6 (1.1%)§	N=229 0%	N=172 2 (1.16%)§	N=145 2 (1.38%)§	NA
Middleton 2005[24]	prospective	223	NR	NR	NR	N/A	N/A
International							
Ngoc 2014[16] Vietnam	prospective	1433	1 (0.07%)	NR	NR	NR	N/A
Goldstone 2012[20] Australia	retrospective	13,345	NR	N=11,855 NR	N= 1441 NR	N=49 NR	N/A
Boersma 2011[22] Curacao	prospective	331	2/331 (0.6%)	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

* NR= not reported

‡numbers of hospitalizations for Gatter study includes those for bleeding and infection in subsequent tables.

^ includes woman with sepsis noted in Table 13, and one woman with chronic pancreatitis, recurrent.

§includes subjects receiving transfusions noted in Table 14.

Source: NDA clinical reviewer table.

Serious infection:

Infections requiring hospitalization or IV antibiotics were rare in the studies. Only three US studies captured this information, with rates ranging from 0-0.015%. Two studies separated this information out by gestational age. In Gatter 2015[13], the two serious infections were in women ≤ 49 days gestation. There were no serious infections in

women at 50-56 or 57-63 days gestation. In Winikoff 2012[19], there was one serious infection in a woman at 57-63 days and none in women at 64-70 days. See Table 13.

Among the international studies, there were five women hospitalized with rates from 0.03-0.07%. This information was not broken down by gestational age. See Table 13.

Table 13: Serious Infection by Gestational Age

Study	Design	Subjects (N)	Serious Infection by gestational age {Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/ not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
USA							
Gatter 2015[13]	retrospective	13,373	2 (0.015%)	N= 8945 2 (0.022%)	N= 3142 0%	N=1286 0%	N/A
Chong 2015[17]	prospective	400	NR*	NR	NR	NR	N/A
Winikoff 2012[19]	prospective	729	1 (0.014%)	N/A	N/A	N=325 1 (0.31%)	N=304 0%
Grossman 2011[36]	prospective	578	NR	N=283 NR	N=103 NR	N=63 NR	N/A
Winikoff 2008[23]	prospective	421	NR	N=213 NR	N=93 NR	N=115 NR	N/A
Creinin 2007[25]	prospective	546	0	N=229 0%	N=172 0%	N=145 0%	N/A
Middleton 2005[24]	prospective	223	NR	NR	NR	N/A	N/A
International							
Ngoc 2014[16] Vietnam	prospective	1433	1 (0.07%)	NR	NR	NR	N/A
Goldstone 2012[20] Australia	retrospective	13,345	4 (0.03%)	N=11,855 NR	N=1441 NR	N=49 NR	N/A
Boersma 2011[22] Curacao	prospective	331	NR	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

*** NR= not reported**

Source: NDA clinical reviewer table.

Transfusion data:

With regard to bleeding requiring transfusion, five of the seven US studies included this information as shown in Table 14. The rates of transfusion range from 0.03-0.7%. Three of the studies provided a breakdown by gestational age. In Gatter 2015[13], there were the following: one woman in the ≤ 49 days group, three in the 50-56 days and zero in the 57-63 days group. In Winikoff 2012[19], there were: two in the 57-63 days group

and 1 in the 64-70 days group. In Creinin 2007[25], there were two women transfused each in the 50-56 days and 57-63 days. Only one international study[20] (Goldstone 2012) reported on transfusions and 11/13,345 women or 0.08% required transfusion.

Table 14: Transfusion by Gestational Age

Study	Design	Subjects (N)	Bleeding Requiring Blood Transfusion by gestational age [Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
USA							
Gatter 2015[13]	retrospective	13,373	4 (0.03%)	N=8945 1 (0.01%)	N=3142 3 (0.1%)	N=1286 0	N/A
Chong 2015[17]	prospective	400	NR	NR	NR	NR	N/A
Winikoff 2012[19]	prospective	729	3 (0.41%)	N/A	N/A	N=325 2 (0.53%)	N=304 1 (0.29%)
Grossman 2011[36]	prospective	578	1 (0.17%)	N=283 NR	N=103 NR	N=63 NR	N/A
Winikoff 2008[23]	prospective	421	NR	N=213 NR	N=93 NR	N=115 NR	N/A
Creinin 2007[25]	prospective	546	4(0.7%)	N=229 0	N=172 2 (0.36%)	N=145 2 (0.36%)	N/A
Middleton 2005[24]	prospective	223	1 (0.45%)	NR	NR	N/A	N/A
International							
Ngoc 2014[16] Vietnam	prospective	1433	NR	NR	NR	NR	N/A
Goldstone 2012[20] Australia	retrospective	13,345	11 (0.08%)	N=11,855 NR	N=1441 NR	N=49 NR	N/A
Boersma 2011[22] Curacao	prospective	331	NR	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

***NR= not reported**

Source: NDA clinical reviewer table.

Ectopic pregnancy:

Ectopic pregnancies were rarely reported in the supporting literature submitted with this efficacy supplement. Only one ectopic pregnancy was reported among 847 patients (0.12%) in Winikoff 2008[23].

Several studies also included less detailed, though still useful, information on adverse events. Ireland et al[15] conducted a retrospective review of 30,146 women undergoing

medical or surgical abortion at ≤ 63 days gestation at Planned Parenthood clinics in Los Angeles between November 1, 2010 and August 31, 2013. The authors reported that 29 women of 13,221 (0.1%) undergoing medical abortion experienced a major complication, which was defined as including: emergency department presentation, hospitalization, infection, perforation and hemorrhage requiring transfusion. The article did not specify the rate of each event. No deaths or ectopic pregnancies were reported in this study. In 2011, Grossman[36] reported on a study of medical abortion provided through telemedicine, in which 578 women seeking abortion services at Planned Parenthood of the Heartland clinics in Iowa were offered in-person services or telemedicine services. The serious adverse event outcomes are reported in Table 12, Table 13 and Table 14 above, but in addition, he reported on adverse events among all medical abortion patients from July 1, 2008 through October 31, 2009 (a wider time frame than the study itself). Four of 1,172 telemedicine patients (0.3%) required a blood transfusion compared to 0.1% of 2,384 in-person patients. These figures were reported in the paper to support study findings of low rates of serious adverse events, including transfusion. Pena (2014)[44] reported on 1,000 women in Mexico who had a medical abortion up to 63 days gestation. Their paper reported that "there were no serious complications as defined by any occurrence that was unexpected, serious, and related to the induced abortion." Upadhyay et al[55] used 2009 through 2010 patient-level billing data from Medi-Cal, California's state Medicaid program, to evaluate the incidence of complications after abortion, including medical abortion. Major complications were defined as those which required hospitalization, surgery or blood transfusion. There were 11,319 medical abortions, with 35 women (0.31%) having a major complication.

Winikoff (2012)[19] provides data on other serious adverse events through 70 days. Regarding hospitalization, there were zero hospitalizations among 350 women receiving medical abortion at 64-70 days compared with 2/379 women at 57-63 days (0.5% rate). There were no serious infections in the 64-70 day group, compared with 1/379 (0.3% rate) in the 57-63 day group. There was one transfusion (1/350=0.3% rate) in the 64-70 day group, compared with 2/379 (0.5% rate) in the 57-63 day group.

Reviewer comments:

(b) (4)

. Serious adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are rarely reported in the literature. The rates, when noted are exceedingly rare, with rates generally far below 1.0% for any individual adverse event. This indicates that medical abortion with the proposed regimen up through 63 days is safe.

[55] Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. Obstet Gynecol 2015;125(1):175-183.

Serious fatal or nonfatal adverse events in the 64-70 days gestation group, were evaluated in one US study (Winikoff 2012)[19]. This study with 379 women in the 64-70 day range is reassuring in that the rates of hospitalization, serious infection and transfusion are no higher than in the lower gestational age ranges. Based on the available safety data on medical abortion in totality, it appears that serious fatal or nonfatal adverse events are very rare through 70 days as well. This regimen should be approved for use through 70 days gestation.

Reviewer's Final Recommendation:

The regimen of mifepristone 200 mg followed by misoprostol 800 mcg buccally in 24-48 hours is safe to approve for use through 70 days gestation.

7.3.3 Dropouts and/or Discontinuations

The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc 2014[16]) to 22% in the Grossman[36] study using telemedicine to deliver medical abortion services. One study noted no differences in demographics between the subjects on whom follow-up was available, compared with those on whom no follow-up information was available. Only two studies evaluated other subgroups of women lost to follow-up. Gatter et al 2015[13] found a higher odds of loss to follow-up with age <18 and with income at or below the federal poverty level. Additionally they noted increased odds of loss to follow-up with increasing gestational age. As compared with women 43-49 days gestation, the Odds Ratio (OR) for loss to follow-up at 50-56 days was 1.17 (95% CI 1.05-1.31) and at 57-63 days was 1.28 (95% CI 1.10-1.48). The Boersma study[22] had a 7% loss to follow-up rate. The rate of loss to follow-up was 6.5% at ≤ 49 days, 7.6% at 50-63 days and 7.7% at 64-70 days. No tests for significance were applied to these numbers. Only one study reported on withdrawals: Winikoff 2012[19] reported that 0.27% of patients withdrew and noted this was similar to rates previously reported in the literature.

Reviewer comment:

There is a wide range of loss to follow-up in the studies submitted with the efficacy supplement. The loss to follow-up rate cannot be reliably linked to method of follow-up, though it is notable that the lowest rate of loss-to-follow-up occurred in the Ngoc trial with telephone follow-up (0.6%) and the highest with abortion services provided via telemedicine (22%). The range of loss to follow-up is well-within the range documented in literature covering real-world abortion practice.[1]

7.4 Significant Adverse Events

The label for misoprostol currently includes a boxed warning against the use past 8 weeks gestation, due to the risk of uterine rupture. The (b) (6) safety reviewer and

(b) (6) conducted separate literature searches on this topic. Chen et al 2008[56] evaluated 488 women with a mean gestational age of 7.8 weeks who received 800 mcg misoprostol as part of a randomized study of misoprostol vs. curettage for early pregnancy failure. They found that 78 (16%) of women in the misoprostol group had previous uterine surgery (>1 C-section or myomectomy). There were no uterine ruptures in that study. Gautam et al[57] reported in 2003 on 66 women up to 60 days' gestation and with previous Caesarean section scar, who received misoprostol 800 mcg for termination and found no uterine ruptures. The literature search also revealed five case reports of uterine rupture.[58, 59, 60 , 61, 62] Of these five cases, three occurred with combined mifepristone/misoprostol dosing. Four women had uterine scars, most commonly from at least one prior cesarean section, and one of them had had a prior uterine rupture in labor. Only one woman had no prior uterine scar (Willmott). In these case reports and studies, women received varying doses of misoprostol ranging from 400 mcg to 600 mcg to 800 mcg, and in two, the women received multiple doses of misoprostol (4 and 5 doses in the Wilmot and Bika reports respectively). The women required surgery to repair the uterus or hysterectomy and transfusion. See Table 15.

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56 Chen BA, Reeves MF, Creinin MD, Gilles JM, Barnhart K, Westhoff C, Zhang J. National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial. Am J Obstet Gynecol 2008;198(6):626. d1-5 doi: 10.1016/j.ajog.2007.11.045. Epub Feb 15, 2008.

57 Gautam R, Agrawal V. Early medical termination pregnancy with methotrexate and misoprostol in lower segment cesarean section cases. J Obstet Gynaecol Res 2003; 29(4):251-256.

58 Khan S, et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. J Obstet Gynaecol 2007;27(8):869-870.

59 Kim JO, et al. Oral misoprostol and uterine rupture in the first trimester of pregnancy: A case report. Reproductive Toxicology 2005;20:575–577.

60 Jwarah E, Greenhalf JO. Rupture of the uterus after 800 micrograms misoprostol given vaginally for termination of pregnancy. BJOG 2000;107:807.

61 Bika O, Huned D, Jha S, Selby K. Uterine rupture following termination of pregnancy in a scarred uterus J Obstet Gynaecol 2014;34(2):198-9. doi: 10.3109/01443615.2013.841132.

62 Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. BJOG 2008;115:1575-1577.

Table 15: Uterine Rupture with Misoprostol Case Reports

Study	GA (weeks)	Mifepristone used?	Dose of Misoprostol	Number of doses of misoprostol	Risk Factor for Rupture
Khan[58]	8	Yes; dose not specified	600 mcg	1	1 prior C-section, 1 prior uterine rupture at 32 weeks
Kim[59]	8	No	400 mcg	1	1 prior C-section
Jwarah[60]	8 2/7	No	800 mcg	1	1 prior C-section
Bika[61]	10 2/7	Yes; 200 mg	800 mcg x 2 doses then 400 mcg x 2 doses	4	2 prior C-sections
Willmott[62]	12 3/7	Yes; 200 mg	400 mcg	5	none

Source: NDA clinical reviewer table.

(b) (6) also conducted a review of FAERS cases from January 1,1965 through October 15, 2015 for reports of uterine rupture with mifepristone alone, misoprostol alone, or a combined regimen, with special interest in cases occurring in women ≤ 10 weeks pregnant (≤ 70 days). The FAERS search retrieved 80 cases of uterine rupture, with 77 citing misoprostol use alone and 3 citing both mifepristone and misoprostol use. No cases of uterine rupture were reported with mifepristone use alone. Vaginal administration of misoprostol was documented in the majority of the cases. The majority of the FAERS cases either occurred in the 3rd trimester of pregnancy, or did not report gestational age. In the cases where the gestational age was not reported, it is likely that most of these cases occurred during the 2nd or 3rd trimester, as many noted the induction of labor as the reason for misoprostol use. The majority of cases also noted at least one additional potential risk factor, with a history of at least one previous c-section, or the use of additional uterotonic drugs (e.g., oxytocin or dinoprostone) being the most commonly reported. The use of misoprostol during the 3rd trimester for the induction of labor, cervical ripening, or both, in women that had at least one previous c-section, was also documented in many cases.

There were only two cases (2.5% of all reports) that reported uterine rupture within the first 10 weeks of pregnancy. In both cases, misoprostol alone was utilized for termination of pregnancy. The first case provided minimal information other than documentation of a 5 week gestation, and an ultrasound noting “an important uterine separation” during an unspecified time after misoprostol (route not specified) administration. The remaining case was also a published case report in which uterine rupture was documented as occurring approximately 2.5 hours after 800 mcg of misoprostol was administered vaginally for cervical preparation prior to surgical termination of pregnancy. The patient was 8 weeks and 2 days pregnant, had a history of a prior c-section, and was of advanced maternal age. (b) (6) concluded that uterine

rupture associated with the use of mifepristone alone, misoprostol alone, or both, is likely a rare event in the 1st trimester.

Reviewer comment:

Based on the scarcity of reported cases in the first trimester of pregnancy, uterine rupture associated with early medical abortion using mifepristone with or without misoprostol is likely rare. There are a three reports of uterine rupture with mifepristone and misoprostol in the first trimester, most of which occurred in women with prior uterine surgery (e.g., a cesarean section).

7.4.1 Submission-Specific Primary Safety Concerns

Summary of requested dosing changes in the NDA Supplement that could affect safety:

1. **Proposing a new dosing regimen that uses mifepristone 200 mg oral and the buccal administration of 800 mcg misoprostol at 24-48 hours after Mifeprex and increasing the gestational age from 49 days to 70 days**

   The Applicant submitted several articles in support of the proposed dosing regimen as well as increasing the gestational age through 70 days using the proposed regimen, including the 24-48 hour interval. See Section 7.3 Major Safety Results for fatal and nonfatal serious adverse events reported with the proposed regimen and gestational age. The data submitted show these events to be exceedingly rare, indicating that the new dosing regimen and increasing the gestational age to 70 days is safe. Please see Section 7.3 Major Safety Results on Nonfatal Serious Adverse Events for a review of this information.

   In further support of changing the dosing interval for misoprostol to 24-48 hours after mifepristone is taken, the Applicant also provided a systematic review by Shaw et al.[63] In this study the authors searched Medline, ClinicalTrials.gov, Popline and the Cochrane Controlled Trials Register and included 20 randomized controlled trials and 9 observational studies. The majority of the studies used the proposed 200 mg dose of mifepristone, but three RCTs and two observational studies used 600 mg of mifepristone. The doses and route of misoprostol administration varied, including doses of 400 mcg, 600 mcg, and 800 mcg, some with repeat doses, and included vaginal, buccal, oral and sublingual routes. There was wide variation in time to administration of the misoprostol, ranging from <24 hours, 24-48 hours, 36-48 hours. Adverse events were not reported consistently. There was no statistically significant difference in nausea, vomiting or diarrhea.

[63] Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. Obstet Gynecol 2013;121(6):1335-1347.

Reviewer comment:

Unlike the efficacy data, which is based on studies that look specifically at individual changes proposed by the Applicant, the adverse event data typically come from studies or reviews that include multiple changes (e.g., dose of each drug, dosing interval, gestational age) simultaneously. Therefore, it is not possible to provide safety data specific to each individual change.

The changing of the dosing interval to 24-48 hours does not appear to increase the risk of serious fatal or nonfatal adverse events or to increase the risk of common adverse events associated with medical abortion.

Reviewer's Final Recommendation:

Based on the available evidence, changing the dosing interval between mifepristone and misoprostol to 24-48 hours is safe to approve, including for use in gestations up through 70 days.

2. Home administration of misoprostol

Currently, the Dosage and Administration section of labeling for Mifeprex requires that patients return to the healthcare provider on Day 3 (two days after ingesting Mifeprex) for misoprostol. The Applicant proposes that the label be changed to allow for home administration of the misoprostol. The Applicant reasons that all published US trials after the initial trial by Spitz et al[26], as well as numerous international trials, included distribution of misoprostol for self-administration at home with evidence of safe and effective medical abortion. The Applicant also emphasizes that women usually start having bleeding within two hours of administration of the misoprostol and home administration gives the opportunity for more privacy in the process.

The Applicant submitted many articles to support this change. See Table 8 for US and foreign studies that enrolled over 30,000 women who administered misoprostol at home. None of the studies directly compare home versus clinic/office administration of misoprostol. Most of the studies include protocols where all of the subjects take misoprostol at home. Gatter[13] and Ireland[15] reported separately on large numbers of clients of Planned Parenthood Los Angeles (13,373 and 13,221 clients respectively, though likely with some overlap, in 2010-2011), while Winikoff (2012[19] and 2008[23]), Grossman[36], Creinin[25] and Middleton[24] reported on smaller numbers of US subjects. Internationally, Goldstone[20] reported on 13,345 medical abortions, while Kopp Kallner[64], Løkeland[65], Chong (2012)[40], Bracken[49], Pena[44],

[64] Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. Human Reprod 2010;25(5):1153-1157.

[65] Løkeland M, Iversen OE, Engeland A, Økland I. Medical abortion with mifepristone and home administration of misoprostol up to 63 days' gestation. Acta Obstet Gynecol Scand 2014;93:647-653.

Ngoc[16], Louie[14], Sanhueza Smith[48], Boersma[22] and Lynd[66] report on smaller numbers of subjects. All of these studies have been reviewed above in Sections Deaths, Nonfatal Serious Adverse Events and Common Adverse Events. This information shows that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the original studies of clinic administration of misoprostol.

Swica et al[50] similarly conducted a non-randomized trial with 301 US women, 139 of whom chose home use of mifepristone and misoprostol and 162 of whom chose clinic administration of mifepristone followed by home use of misoprostol. The majority of women (74%) who chose home use took the mifepristone at the appointed 6-48 hour window; for those who took it at a different time than that planned with their provider, the median interval was 25 hours. Over 90% of women in both groups took the misoprostol at the scheduled time, and none waited past 72 hours to take the misoprostol. There were no significant differences in the mean number of days of work or school missed or dependent care needed. Most women made no additional calls (85% for home use group and 90% for office use group) or unscheduled visits to the doctor's office (96% for home use group and 99% for office use group).

The Applicant also submitted a commentary by Gold and Chong[67], in which they discuss benefits of home administration of Mifeprex and misoprostol. They cite the convenience of scheduling for women, the possibility of greater autonomy and privacy, the lack of burden on staff, and the safety.

Reviewer comment:

Home use of misoprostol has been evaluated as part of the proposed protocol in studies including well over 30,000 patients, as well as in dedicated studies of home use of mifepristone and misoprostol. The studies demonstrate that women take the misoprostol at the recommended time. The safety profile is acceptable, with rates of adverse events equal to or lower than those with the approved regimen requiring in-office dispensing of misoprostol. The studies, including those of home use of mifepristone and misoprostol, show increased convenience, autonomy and privacy for the woman, a smaller impact on their lifestyles, and no increased burden on the healthcare system. The safety data on the home use of misoprostol are adequate to support revision of labeling.

[66] Lynd K, Blum J, Ngoc NTN, Shochet T, Blumenthal PD, Winikoff B. Simplified medical abortion using a semi-quantitative pregnancy test for home-based follow-up. Int J Gynecol Obstet 2013;121:144-148.

[67] Gold M, Chong E. If we can do it for misoprostol, why not for mifepristone? The case for taking mifepristone out of the office in medical abortion. Contraception 2015;92:194-196.

Reviewer's Final Recommendation:

Based on the available data, home use of misoprostol is safe to approve.

3. Repeat dose of misoprostol if needed.

The Applicant reasoned that studies include an option for a repeat dose of misoprostol to allow women to avoid a surgical procedure if possible and that this is a safe way to treat an incomplete medical abortion. The Applicant submitted two articles on the repeat use of misoprostol, one randomized trial and one systematic review, that were relevant to this safety review (other articles[12, 17, 22] did not present safety data stratified by number of misoprostol doses). Only one randomized trial reviewed the safety of repeat misoprostol. Coyaji et al[68] conducted a randomized controlled trial of 300 women seeking medical abortion in India. After taking mifepristone, women in one group took 400 mcg misoprostol followed by placebo 3 hours later, while women in the other group took two doses of 400 mcg misoprostol 3 hours apart. As discussed in the efficacy portion of this review, there was no significant difference in the complete abortion rate between the groups; however, the repeat misoprostol reduced need for surgical intervention. Before discharge home, there was no significant difference in the adverse effects observed—similar percentages of women experienced cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). More women in the repeat dose arm experienced moderate to severe cramping than women in the single dose arm on Day 4 (24% versus 15%, p=0.032) and on Day 7 (10% versus 4%, p=0.006).

Gallo[69] performed a systematic review of data relating to the safety and efficacy of more than one dose of misoprostol after mifepristone for medical abortion. The search yielded three randomized controlled trials that studied medical abortion ≤ 63 days. The studies included doses of mifepristone ranging from 200 mg to 600 mg followed by misoprostol 6 to 48 hours later, in doses ranging from 400 mcg to 800 mcg via the oral, sublingual or vaginal routes. In two trials, all subjects received repeat misoprostol—in one, three hours later, while in the other study subjects received misoprostol twice a day for days 4-10. In the third trial, subjects only received repeat misoprostol if there was still a gestational sac present. The only side effects discussed in the trials were diarrhea, which was more common in those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported <1%.

There is a good deal of literature on the use of misoprostol alone for medical abortion and in those regimens, doses of up to 800 mcg repeated in three hours have been

[68] Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? BJOG 2007;114:271-278.

[69] Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. Contraception 2006;74:36-41.

used. In a study by Blum et al[70], misoprostol only, given as two doses of 800 mcg three hours apart, was compared to mifepristone-misoprostol medical abortion where only one dose of 800 mcg misoprostol was administered. The two groups had similar rates of nausea, vomiting, fever and chills. Subjects in the repeat misoprostol group had more diarrhea than in the mifepristone-misoprostol group (83.9% vs. 61.2%, p<0.001). Please see Section 7.4 Significant Adverse Events for additional discussion on safety concerns with repeat doses of misoprostol.

Reviewer comment:

There are few articles concerning the safety of repeat misoprostol after mifepristone administration. Generally, the success of mifepristone-misoprostol medical abortion renders the need for a second dose of misoprostol to be relatively uncommon. In studies of misoprostol alone given using a single repeat dose, there is an increased risk of the common adverse event of diarrhea. There have been rare reports of uterine rupture in women with a prior uterine scar who receive repeated doses of misoprostol.

Reviewer's Final Recommendation:

Based on the available data, the option for repeat misoprostol in women whose pregnancy has been terminated, but who have not completely expelled the pregnancy is safe and should be approved. For women whose pregnancy is ongoing at follow-up, surgical intervention is recommended, rather than repeated misoprostol. The rare reports of uterine rupture in women with a prior uterine scar who receive repeated doses of misoprostol is discussed in labeling.

4. Follow-up timing and method: follow-up is needed, but not necessarily in the clinic or licensed healthcare provider's office at 14 days after mifepristone administration

The Dosage and Administration section of the current approved label for Mifeprex stipulates that patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred. The Applicant acknowledges that follow-up is important to diagnose and treat complications, and to ensure complete abortion or identify ongoing pregnancies. However, the Applicant proposes to change the labeling to state that the provider should perform an assessment at 1-2 weeks, in order to broaden the timeframe and method used, to give patients and providers more flexibility and reduce loss to follow-up rates. Use of ultrasound, serum and urine pregnancy testing (semi-quantitative, and quantitative) and telephone calls have all been evaluated in the literature as options for follow-up of patients after medical

[70] Blum J, Raghavan S, Dabash R, Ngoc NTN, Chelli H, Hajri S, Conkling K, Winikoff B. comparison of misoprostol-only and combined mifepristone-misoprostol regimens for home-based early medical abortion in Tunisia and Vietnam. Int J Gynecol Obstet 2012;118:166-171.

abortion. Grossman and Grindlay[71] conducted a systematic review of the literature on alternatives to ultrasound for medical abortion follow-up. They identified eight studies, but found that outcomes of interest (ongoing pregnancy) were rare with medical abortion and not consistently defined across studies. Nonetheless, they found that serum hCG, a low sensitivity urine pregnancy test combined with a standardized assessment with multiple questions about women's symptoms, or standardized telephone follow-up, perhaps followed by high-sensitivity urine pregnancy test, all had sensitivities ≥90% and negative predictive values (NPVs) ≥99% and they resulted in a proportion of "screen positives (or women who had a self-assessment of ongoing pregnancy and had an unscheduled visit) ≤33%."

This reviewer analyzed relevant studies that were submitted by the Applicant and referenced in the Grossman and Grindlay assessment.[71] Perriera et al[21] conducted a prospective cohort study of 139 US women with ≤63 days gestation undergoing medical abortion at one center. Up to three attempts were made to phone subjects 7 days after taking mifepristone. The subjects were asked to confirm when they took misoprostol and generally to describe their experience. They were then asked a series of five standardized questions to assess for expulsion, including:

1 Did you have cramping and bleeding heavier than a period?
2 Did you pass clots or tissue?
3 What was the highest number of pads you soaked per hour?
4 Do you still feel pregnant now?
5 Do you think you passed the pregnancy?

If the clinician or the subject did not think the pregnancy had passed, the subject was asked to return to the center for an ultrasound within 7 days. If there was an ongoing pregnancy, women were offered additional misoprostol or a D&C. If the clinician and subject believed the pregnancy had passed, she was instructed to begin birth control or schedule a visit for injectable, implantable or intrauterine contraception. On Day 30, the subject was to perform a urine pregnancy test. Follow-up was obtained for 97.1% of subjects. Four subjects did not complete follow-up (2.9%)—one was never reached by phone, three were and two of them had positive pregnancy tests while one had an inconclusive test. These three never returned for an in-person visit and outcomes are not available on them. The sensitivity for correctly predicting an expelled pregnancy (completed abortion) was 95.9%, specificity was 50%, positive predictive value 97.5% and negative predictive value 37.5%. This study suggests that clinicians and subjects are almost always correct when they believe a pregnancy has passed. The loss to follow-up rate was not higher than for standard medical abortion follow-up.

Fiala et al[72] compared hCG with ultrasound for verification of completed abortion in 217 women ≤49 days with intrauterine pregnancy in Scotland. Successful expulsions were

[71] Grossman D, Grindlay K. Alternatives to ultrasound for follow-up after medication abortion: a systematic review. Contraception 2011;83:504-510.
[72] Fiala C, Safar P, Bygdeman M, Gemzell-Danielsson K. Verifying the effectiveness of medical abortion;

consistent with a marked decline in hCG values at follow-up. Using 20% of the initial value as cut-off at follow-up gave a high sensitivity. It allowed correct diagnosis in 98.5% of the patients with successful expulsion. When 20% of the initial hCG value was used as cut-off, a positive predictive value for successful expulsion was 99.5%. If the reduction of the hCG level was less than 80%, the negative predictive value was 50% and further evaluation was warranted. By contrast, the reliability of ultrasound examination in diagnosing successful expulsion was 89.8%.

Lynd et al[66] studied 300 women at ≤ 63 days gestation who underwent medical abortion in Vietnam. Women were given mifepristone and sent home with misoprostol and a semi-quantitative urine pregnancy test, a urine cup, instructions and a questionnaire. They were to take the urine test, record their impression of the results and complete the questionnaire on the morning of an in-person follow-up visit 2 weeks after mifepristone administration. Fifty-four women (18.5%) still felt pregnant at the follow-up visit, but only 11 of the semiquantitative urine tests indicated ongoing pregnancies. All 11 correctly identified ongoing pregnancies, with 100% sensitivity and 89.7% specificity. Ten of the 11 women with an ongoing pregnancy understood in-person follow-up was necessary.

Similarly, Cameron et al[73] reported on 1791 women undergoing medical abortion in Scotland, 1,726 (96%) of whom chose self-assessment with a low-sensitivity urine pregnancy test, instructions on how to interpret it, and signs/symptoms of ongoing pregnancy. The rest of the women chose in-clinic follow-up with an ultrasound or a phone call. Eight women in the self-assessment group had ongoing pregnancies, but only four of them had a positive low-sensitivity pregnancy test at the appointed time—within 4 weeks. Of the four who did not follow up in 4 weeks, two had a positive or invalid pregnancy test within two weeks after the medical abortion and should have presented for care, and two reported their pregnancy test was negative and did not present for care. All has successful termination either with repeat medical dosing or surgical aspiration. Most women presented within four weeks, but two women presented only after two missed menses. The delayed follow-up was not different from that for an in-person visit or an ultrasound.

Reviewer comments:

While the number of articles is not extensive, they include almost 2,400 subjects. The Applicant demonstrates that alternatives to in-clinic follow-up are effective and safe, detecting most of the ongoing pregnancies so that women can get needed treatment. It appears that, using standardized questionnaires or instructions or a telephone call along with a low or high sensitivity pregnancy test, ongoing pregnancies can be detected allowing for further treatment. There is some loss-to-follow-up, but the rates do not appear to exceed those associated

ultrasound versus hCG testing. Eur J Obstet Gynecol Reprod Biol 2003;109;190-195.
[73] Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? Contraception 2015;91:6-11.

with a planned in-clinic follow-up. Women should be allowed to have an in-person visit if desired, but also allowed the flexibility of other options if desired.

It is important to note that since 2005, Planned Parenthood Federation of America has waived the follow-up visit if it poses undue hardships owing to distances from abortion facilities or other reasons, and women manage their follow-up with serial hCG testing.[74] From the clinical reviewers' perspective, this is safe and acceptable. We further note that the NAF 2015 guidelines (page 23) state the following:

> **"Success of the medical abortion must be assessed by ultrasonography, hCG testing, or by clinical means in the office or by telephone. If the patient has failed to follow-up as planned, clinic staff must document attempts to reach the patient. All attempts to contact the patient (phone calls and letters) must be documented in the patient's medical record."**

The ACOG 2014 Practice Bulletin[1] on management of early MAB states "Follow-up after receiving mifepristone and misoprostol for medical abortion is important, although an in-clinic evaluation is not always necessary." Several options for follow up without an office/clinic visit are discussed and no specific method or algorithm is definitely recommended (i.e., it is left to the discretion of the provider and patient).

Reviewer's Final Recommendation:

Based on the available evidence, flexibility in the timing and method of follow-up is safe to approve.

7.5 Supportive Safety Results

7.5.1 Common Adverse Events

According to the currently approved Mifeprex label,[75] common adverse events include the following:

- Vaginal bleeding up to 16 days, with 8% of women experiencing bleeding up to 30 days. 4.8% of women in the original US trials and 4.3% in the original French trials required administration of uterotonic agents to control the bleeding. Only 1% of women required intravenous fluids and 1% required curettage. In the original French trials, 5.5% of women had a drop in hemoglobin of more than 2 g/dL.
- Abdominal pain in 96% of US women
- Uterine cramping in 83% of French women
- Nausea in 43-61%, vomiting in 18-26%

[74] Fjerstad M. Figuring out follow-up. Mife Matters. Planned Parenthood Federation of America/Coalition of Abortion Providers 2006;13:2–3.

[75] http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.htm

- Diarrhea in 12-20%
- Headache in 2-31%
- Dizziness in 1-12%

A review of the literature submitted in the efficacy supplement, which includes Mifeprex at the proposed dose but also includes misoprostol administered buccally, vaginally or orally, reveals the following. Table 16 addresses bleeding that did not require transfusion (which is covered inTable 14: Transfusion by Gestational Age above), but was still significant in terms of requiring another intervention or in terms of a decrease in measured hemoglobin. Most of the studies include subjects up to 63 days' gestation, with the exception of Middleton 2005[24], which includes subject to 56 days, and Sanhueza Smith 2015[48] and Winikoff 2012[19], which include subjects through 70 days.

Table 16: Bleeding and Cramping in Literature

Study	N	Maximal Gestational Age	Route of misoprostol administration	Adverse Event Rate (%)		
				Bleeding requiring intervention*	Bleeding with drop in hemoglobin > 2g/dL	Cramping/pain
Middleton 2005[24]	216	56 d	buccal	4.2	NR	NR
Coyaji 2007[68]					NR	87-89
Løkeland 2014[65]				4.9	NR	96.6
Kopp Kallner 2010[64]	395	63 d	vaginal	0.5	NR	NR
Pena 2014[44]	971	63 d	Buccal	1.7	NR*	NR
Ngoc 2014[16]	1433	63 d	buccal	0.07	NR	NR
Gatter 2015[13]	13,373	63 d	buccal	1.8	NR	NR
Ireland 2015[15]	13,221	63 d.	buccal	1.8	NR	NR
Winikoff 2012[19]	729	70 d	buccal	1.1	NR	NR
Sanhueza Smith 2015[48]	960	70 d	buccal	1.7	NR	NR

***Intervention includes aspiration or uterine evacuation, use of uterotonics, intravenous fluids**
***NR=not reported**

Source: NDA clinical reviewer table.

Reviewer Comments:

Given that Mifeprex and misoprostol are taken to terminate an intrauterine pregnancy, vaginal bleeding and cramping or abdominal pain are an expected

and necessary part of the process; therefore, these should only be considered adverse events if the amount of bleeding or pain exceeds what would be expected for such a process. The rate of bleeding requiring intervention is low and ranges from 0.5% to 4.2%, with the rates in the largest studies being around 1.8%. Two articles parsed the bleeding requiring intervention by gestational age. In Sanhueza Smith et al.[48] the rate was 1.1% (7/622) among women ≤ 56 days, 4.2% (8/190) in women 57-63 days and 1.4% (2/148) in women 64-70 days. In Gatter 2015[13], the rate was 0.65-1.43% up to 49 days, 2.04% in women 50-56 days, and 2.49% in women 57-63 days. These differing numbers from the two studies do not reveal a trend toward bleeding requiring intervention with increasing gestational age, specifically even through 70 days.

No articles submitted discussed a drop in hemoglobin of > 2 g/dL, most likely because routine laboratory studies are not obtained in medical abortion unless anemia or a medical illness is reported or suspected. Also not surprisingly, pain and cramping are an expected part of the medical abortion process, so most studies do not comment on the percentage of women who experience this.

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Table 17: Common Adverse Events in Literature

Study	N	Maximal GA (days)	Route of Misoprostol	Adverse Event Rate (%)							
				nausea	vomiting	diarrhea	fever	chills	headache	dizziness	weakness
Middleton 2005[24]	216	56 d	Buccal	70	37	36	42	NR	44	41	51
Blum 2012[70]			buccal	45.9	37.8	61.2	28.2	30.6			NR
Coyaji 2007[68]				1	0-2	NR*	NR	NR			NR
Kopp Kallner 2010[64]	395	63 d	vaginal	87.1	57.3	6.3	26.3	NR	4.1	3.6	2-3.1
Louie 2014[14]	860	63 d	buccal	38-53	13-25	1-3	15-23†				NR
Pena 2014[44]	971	63 d	buccal	NR	NR	7.8	8.9†	†	NR	NR	14.3
Creinin 2007[25]	544	63 d	vaginal	9.4	5.7	4.8	10.3†	†	6.6	6.8	NR
Chong 2012[40]	563	63 d	buccal	47	22	NR	33†	†	33	24	42
Winikoff 2012[19]	618	70 d	buccal	50.8	40.6	17.6	11.2	23.5	NR	NR	NR
Sanhueza Smith 2015[48]	960	70 d	buccal	27	23	44.6	46†	†	14.3	9.7	21

GA = gestational age; *NR= not reported. † includes fever and chills, which were grouped together

Source: NDA clinical reviewer table.

Reviewer comment:

The range of reported percentages for each adverse event is wide, with some studies reporting virtually no patients experiencing nausea, vomiting or diarrhea, while others report at least half of subjects suffering these side effects. Only the Winikoff 2012[19] article parses out these side effects by gestational age (57-63 days versus 64-70 days). There is no statistically significant difference in the rates of any side effect between gestational age group except for vomiting, where 35.8% of women 57-63 days had vomiting and 45.7% of women 64-70 days did (p=0.008). It is hard to determine a value that could be used in labeling based on these wide variations, but the adverse events are common, expected and well-known with the medical abortion regimen and the ranges should be reported in labeling.

7.5.2 Laboratory Findings

Mifepristone with misoprostol is a well-established regimen for termination of pregnancy. Few laboratory tests are necessary before use of the regimen. Those that are commonly performed include confirmation of pregnancy (urine or serum pregnancy testing) as well as Rh testing (unless it has been previously documented), such that RhD immunoglobulin can be administered as indicated. Pre-medical abortion assessment of hemoglobin or hematocrit is indicated when anemia is suspected. Routine follow-up laboratory testing is also not indicated unless dictated by the patient's clinical condition, for example, heavy bleeding or signs of infection. Lab results are not typically reported in the literature, except for when studies look at decreases in hemoglobin related to bleeding.

7.5.3 Vital Signs

Vital signs are not typically reported in the literature on medical abortion.

7.5.4 Electrocardiograms (ECGs)

Mifepristone used with a prostaglandin analogue has been approved for medical termination of pregnancy since 1988 in France and subsequently in many countries around the globe. It has been well-established that doing an ECG prior to MAB is not standard procedure. It can be done if individual circumstances warrant its use. Literature does not typically report on ECGs.

7.5.5 Special Safety Studies/Clinical Trials

The pediatric studies are addressed in Section 7.6.3.

7.5.6 Immunogenicity

NA to this review

7.6 Other Safety Explorations

This section is not relevant to this application.

7.6.1 Additional Safety Evaluations

7.6.2 Human Carcinogenicity

The Applicant submitted no new data on human carcinogenicity.

7.6.3 Human Reproduction and Pregnancy Data

As noted in the efficacy portion of this review, some women who use Mifeprex do have ongoing pregnancies. Most of these are treated with an aspiration or a surgical evacuation of the uterus; there is little information on outcomes of ongoing pregnancies not terminated by another method. At the time of approval of the drug, the Applicant agreed to two postmarketing commitments, including one to conduct a surveillance study of the outcomes of ongoing pregnancies. On January 11, 2008, the Applicant was released from this commitment due to the lack of an adequate number of women enrolled. The Applicant explained that the small number was due, in part, to the requirement that the patients consent to participation *[in the surveillance study]* after seeking a pregnancy termination.

A review of all of the articles submitted by the Applicant for outcomes of ongoing pregnancies after mifepristone administration yielded minimal information. There is one article reporting a case of a fetus with sirenomelia, a cleft palate and lip, micrognathia, and hygroma; this infant was born to a woman who had received mifepristone as RU 486 at 18 weeks and was reported to Roussel-Uclef in France in 1989.[76] A prospective observational study[77] from fifteen French pharmacovigilance centers followed women exposed to mifepristone in the first trimester between1997 and 2010. The study included pregnant women who sought counseling on mifepristone exposure from a pharmacovigilance center or Paris Teratology Information Service (TIS). A total of 105 pregnancies were exposed to mifepristone in the first trimester; 46 to mifepristone alone, and 59 to mifepristone and misoprostol. The mean gestational age at exposure was 7.9 weeks; 81% were exposed between weeks 5 and 9 of gestation. About 40% of patients received 200 mg of mifepristone while about 50% received 600 mg. Of the patients who received both mifepristone and misoprostol, 48 received repeat misoprostol with four receiving 1200–2000 mcg of misoprostol, a significantly higher dose than recommended. Among all exposed women, there were 94 live births (90.4%),10 (9.6%) miscarriages (including one with a major malformation of major hydrocephalus associated with adductus thumb and a normal karyotype) and one patient had an elective termination of pregnancy for the subsequent diagnosis of trisomy 21. Eight of the ten miscarriages occurred in the mifepristone-only group; however, after potential confounding factors such as maternal age, gestational age at inclusion,

[76] Pons JC, Papiernik E. Mifepristone teratogenicity. Lancet 1991;338(8778):1332-3.

[77] Bernard N, Elefant E, Carlier P.Tebacher M, Barjhoux CE, Bos-Thompson MA, Amar E, Descotes J, Vial T. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. BJOG 2013;120:568–575.

drug exposure, and mifepristone dose were controlled for by logistic regression, the rate of miscarriage did not differ across mifepristone only versus mifepristone-misoprostol groups (p= 0.08). Among the live births, the mean gestational age at delivery was 39.5 weeks and there was no difference in birth weights between groups. The overall rate of major congenital malformations among the 95 examinable cases was 4.2% (95% CI 1.2–10.4%), with two cases among 38 patients exposed to mifepristone alone, and two cases among 57 patients exposed to both mifepristone and misoprostol. Three of the four major congenital malformations occurred with exposure to 600 mg of mifepristone, while one occurred in exposure to 400 mg of mifepristone. The malformations included:

- Claude Bernard–Horner syndrome with stridor
- Hydrocephalus with triventricular dilatation and adductus thumb (miscarriage patient noted above)
- Möbius syndrome
- Retrognathism, slight cleft palate, trismus, swallowing disorder, club foot with four toes, incomplete genital development and mild hypoplasia of the cerebellar vermis

The authors posit that the cases of major malformations in patients exposed to mifepristone alone could be explained by associated medical conditions, for example, the case of congenital Claude Bernard Horner syndrome could have been related to traumatic vaginal delivery of a high birth weight newborn, a well-recognized cause of this syndrome, while the spontaneously aborted hydrocephalic fetus may have been caused by streptococcus B chorioamnionitis, which was subsequently confirmed on pathological examination, or be an X-linked hydrocephalus. The authors also note that the two cases of major malformations in patients exposed to both mifepristone and misoprostol were consistent with malformations described after exposure to misoprostol alone. The authors concluded that major malformations after first-trimester exposure to mifepristone is only slightly higher than the expected 2–3% rate in the general population, which was reassuring regarding the risk evaluation for continuation of pregnancy after mifepristone exposure.

There are reports that misoprostol can result in congenital anomalies when used during the first trimester, including defects in the frontal or temporal bones, limb abnormalities with or without Mobius syndrome.[1] The Korlym label notes in Important Safety Issues with Consideration to Related Drugs: “In a report of thirteen live births after single dose mifepristone exposure, no fetal abnormalities were noted.”

Reviewer Comment:

There are anomalies associated with the use of misoprostol in the first trimester. The risk of teratogenic effects with a continued pregnancy after a failed pregnancy termination with Mifeprex in a regimen with misoprostol is unknown. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with Mifeprex in a regimen with misoprostol, but it is not clear if this just represents the usual background rate of birth defects.

As discussed above, FDA requested at the time of initial approval that the Applicant conduct a surveillance study of the outcomes of ongoing pregnancies. The Applicant was subsequently released from this commitment because it had been unable to enroll a sufficient number of women with ongoing pregnancies after an attempted medical abortion in the surveillance study.

7.6.4 Pediatrics and Assessment of Effects on Growth

The Applicant submitted no new data on assessment of effects on growth in pediatric patients. The Applicant did submit data on efficacy and safety of medical abortion in adolescents, using the proposed regimen of 200 mg oral Mifeprex followed by 800 mcg buccal misoprostol 24-48 hours later at home, in order to satisfy requirements for PREA. Gatter et al (2015)[13] included data on 322 adolescents. (b) (6), (b) (4) The adolescent efficacy was similar to that of all older women; this implies that compliance in taking the misoprostol dose properly at home was also acceptable. The study included adolescents aged 11-16 per Table 18 below:

Table 18: Age of Adolescents Undergoing Medical Abortion

Age	# Subjects
11	1
12	1
13	2
14	20
15	82
16	216

Source: (b) (6), (b) (4) **NDA 20687s20**

(b) (4), (b) (6) As is evident in the table, no adolescents had a hospitalization, severe infection or hemorrhage which required a transfusion.

Table 19: Serious Adverse Events in Adolescents vs. Adults

	Under 17	17+	All
Transfusion	0.00% (0/251)	0.03% (4/13,122)	0.03% (4/13,373)
Hospitalization	0.00% (0/251)	0.05% (7/13,122)	0.05% (7/13,373)
Infection	0.00% (0/251)	0.02% (2/13,122)	0.01% (2/13,373)

Source: (b) (6), (b) (4) **NDA 20687s20**

In 2011, Niinimäki et al[54] published a retrospective cohort study of the Finnish abortion registry from 2000-2006, in which they evaluated the rates of adverse events in 3,024

adolescents and 24,006 adult women undergoing medical abortion (regimen unspecified). The study population included women ≤ 20 week's gestation; 84.6% of the adolescents were ≤ 12 weeks, while 86.6% of the adults were ≤ 12 weeks. Adolescents ranged in age from 13-17, with a mean age of 16.1 years. The study showed that after adjustment for parity, previous abortion, marital status, types of residence, duration of gestation and year of abortion, in adolescents, the adjusted ORs were significantly lower for hemorrhage (0.87, 95% CI 0.77 to 0.99), incomplete abortion (0.69, 95% CI 0.59 to 0.82) and surgical evacuation (0.78, 95% CI 0.67 to 0.90) compared to adults. There was no significant difference in the OR for infection (0.97, 95% CI 0.73 to 1.30).

Phelps[53] had previously conducted a pilot study in 28 adolescents aged 14-17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. As reported in Section Subpopulations, 100% of study subjects had a complete abortion, with five not requiring misoprostol. There were no serious adverse events. Subjects noted common expected adverse events including bleeding (100%), cramping (95%), nausea (62%), and vomiting (43%).

It is also important to consider adherence to the proposed regimen (including taking misoprostol at a location other than the clinic) and adherence to follow-up among adolescents versus adults.

There are no data specifically comparing adherence to the regimen among adolescents <17 with women ≥17 years old. The Gatter[13] study clearly demonstrates the efficacy and safety is the same for both age groups, suggesting that there is no clinically significant difference in adherence to the regimen between age groups. The Goldstone[20] article included 8 subjects aged 14 and 931 subjects aged 15-19. The efficacy and safety are not separated out by age; however, all subjects did take the proposed regimen and overall efficacy and safety is reassuring, indicating that adolescents and adults alike likely did adhere to the mifepristone and misoprostol regimen in a safe and effective way.

Regarding adherence to follow-up, four articles included 346 subjects <17 years old. Ngoc[16] is based in Vietnam and Cameron[73] is based in Scotland, while Gatter[13] and Horning[78], are US-based studies. (b) (4), (b) (6) . The difference in the follow-up rate for the combined data is 6.5%. The Gatter study accounts for 85% of all patients being compared. The difference in follow-up adherence is not clinically relevant as there is no difference in efficacy between the two age groups.

Table 20: Adherence to Follow-Up Among Adolescents vs. Adults

	<17 years old			≥17 years old		
	N	# Adherent	Adherence %	N	# Adherent	Adherence %
Gatter[13]	322	251	78.0%	15,517	13,122	84.6%
Cameron[71]	5	4	80.0%	607	516	85.0%
Ngoc[16]	1	1	100.0%	1,406	1,345	95.7%
Horning[78]	18	16	88.9%	846	648	76.6%
TOTAL	346	272	78.6%	18,376	15,631	85.1%

Reviewer Comment:

Medical abortion in adolescents appears to be at least as safe, if not safer, as in adult women. Adolescents appear able to comply with the regimen, including use of misoprostol outside of the clinic setting, as well as with alternative follow-up methods. These data support the safety of Mifeprex in adolescents and satisfy requirements for PREA. No information on safety and efficacy of use in premenarchal girls is required, as the medication is not indicated in that subset of the pediatric population.

Reviewer's Final Recommendation:

The available evidence supports that Mifeprex and the new proposed dosing regimen are safe to use in adolescents.

7.6.5 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant submitted no new data on overdose, drug abuse potential withdrawal and rebound.

7.7 Additional Submissions / Issues

Summary of additional changes in labeling that may affect safety of Mifeprex

1. Change in labeled time for expulsion from 4-24 hours to 2-24 hours

The Applicant proposes to change the time to expulsion described in the labeling from 4-24 hours to 2-24 hours post misoprostol to more accurately reflect the data and real-life experiences with the drug. The Applicant reasons that in the large US trial upon

[78] Horning EL, Chen BA, Meyn LA, Creinin MD. Comparison of medical abortion follow-up with serum human chorionic gonadotropin testing and in-office assessment. Contraception 2012;85:402-407.

which labeling is based (Spitz, 1998[26]), the median time to expulsion was 4 hours. Indeed, in that study, women were observed for several hours after misoprostol administration, and during the four hours of observation, 49% of the women expelled the products of conception, and 60% had by the fifth hour. Several studies are provided to corroborate this. Only one uses buccal misoprostol; however, the misoprostol was administered within 5 minutes of the Mifeprex, not at the 24-48 hour interval as proposed in this supplement. Nonetheless, in this trial, Lohr[79] found the median time to onset of cramping to be 2 hours (range 10 minutes to 13 hours) and bleeding to be 3 hours (range 9 minutes to 11 hours). This shorter duration to expulsion is also seen in several other pilot studies submitted where subjects took vaginal misoprostol immediately or within 6-8 hours of mifepristone. If the focus is shifted to the randomized controlled studies that report times to onset of bleeding and cramping and include vaginal misoprostol, we find data confirming the timing of expulsion in the 2-24 hour window proposed by the Applicant. Creinin[25] noted a median time to onset of cramping of 1.7 hours and to onset of bleeding of 2 hours after misoprostol (administered 24 hours after Mifeprex). In a similar study[80] comparing misoprostol administered 24 vs. 6-8 hours after Mifeprex, the median time to onset of cramping was 1.5 hours and to bleeding was 2 hours in women with misoprostol given 24 hours after Mifeprex.

Reviewer comment:
The data from vaginal and buccal administration of misoprostol around 24 hours after mifepristone support the assertion that bleeding and cramping begin before the 4 hour mark that is currently labeled. Therefore the label should be revised to make this clearer. Median times seem to be around 1.5 to 2 hours. It is reasonable to label the time to expulsion 2-24 hours, but it could be labeled as beginning even earlier. A clearer label will help providers better counsel patients and patients can better select an appropriate time frame within the 24-48 hour window to take their misoprostol and can be prepared when the expulsion starts.

Reviewer's Final Recommendation:
Based on the available evidence, it is acceptable to revise the label so that it notes that the time to expulsion after misoprostol dosing is 2-24 hours.

2. Use of the term "(b) (4)

The Applicant proposes to use the term "(b) (4) in place of all other terms in labeling and in the REMS materials, for consistency and (b) (4) The Applicant

[79] Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD. Oral mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study. Contraception 2007;76:215-220.

[80] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004;103:851-859.

submitted an article demonstrating that nurse practitioners, certified nurse midwives and physician assistants can safely provide aspiration abortion.[81] The Division asked the Applicant to provide articles specifically addressing the provision of medical abortion services by non-physician practitioners, since that is the issue at hand.

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies took place in varying settings (urban, rural, international, low resource). The efficacy results are discussed in Section 6.1.10.

Regarding the safety of medical abortion provided by non-physician health care providers, a systematic review by Renner[82] identified five studies with a total of 8,908 subjects. A RCT in Nepal included 1,104 of those subjects, comparing medical abortions by nurses or auxiliary nurse midwives with those offered by physicians. Outcome data on 1,077 women showed no serious complications (hemorrhage requiring transfusion or condition necessitating hospitalization) and the rate of ongoing pregnancy or incomplete abortion did not vary by physician versus midlevel provider. Also in Nepal, Puri et al[83] described training female community health volunteers to provide education, and training auxiliary nurse midwives to provide medical abortion in intervention districts, and compared knowledge and medical abortion outcomes with those in neighboring districts where there were no interventions. Medical abortions were performed on 307 women in the intervention areas and 289 women in the comparison areas. There were five incomplete abortions (1.6%) in the intervention areas, treated with manual vacuum aspiration by the auxiliary nurse midwives, and 7 (2.4%) incomplete abortions in the comparison areas. The difference was not statistically significant. Kopp Kallner[84] conducted a randomized controlled equivalence trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. The trial showed fewer complications for the nurse midwife group, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, p=0.14).

[81] Weitz TA, Taylor D, Desai S, Upadhyay UD, Waldman J, Battistelli MF, Drey EA. Safety of aspiration abortion performed by nurse practitioners, certified nurse midwives, and physician assistants under a California legal waiver. Am J Public Health 2013;103:454-461.

[82] Renner R-M, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care: a systematic review. BJOG 2013;10:23-31.

[83] Puri M, Tamang A, Shrestha P, Joshi D. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. Reproductive Health Matters 2015;Suppl(44):94-103.

[84] Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell-Danielsson K. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomized controlled equivalence trial. BJOG 2015;122:510-517.

There were no serious complications and no blood transfusions in the study. There was no difference in unscheduled visits. Nurse midwives did call for more second opinions (26%) versus doctors (4%). Olavarrieta[85] conducted a randomized controlled non-inferiority trial in Mexico City abortion clinics. Eight physicians and seven nurses who had not previously independently provided medical abortion care received 1.5 weeks of training. A total of 1,088 women were randomized to two groups of providers. Nurses were not found to be inferior to physicians in the provision of abortion care. There was only one serious adverse event in the physician group, a woman requiring admission and surgical aspiration for heavy bleeding. Nurses requested consultation with an experienced obstetrician in 9 cases, whereas physicians requested consultation only twice.

Reviewer Comments:

The Applicant provided data from over 3,200 women in randomized controlled trials and data on 596 women in prospective cohorts comparing medical abortion care by physicians versus nurses or nurse midwives. The studies were conducted in varying settings (international, urban, rural, low-resource) and found no differences in efficacy, serious adverse events, ongoing pregnancy or incomplete abortion between the groups. Two studies did show that nurses or nurse midwives called for more second opinions than physicians, but these numbers were a small portion of the total subjects included.

Midlevel providers in the United States, such as nurse practitioners, nurse midwives and physician assistants currently provide family planning services and abortion care, including medical abortion care, under the supervision of physicians. The data here demonstrate that it would be safe to allow healthcare providers who are licensed to prescribe medications and who meet the criteria in the REMS to become certified to provide medical abortion care with Mifeprex and misoprostol. Midlevel providers are already practicing abortion care under the supervision of physicians, and the approved labeling and the REMS Prescriber's Agreement already stipulate that prescribers must be able to refer patients for additional care, including surgical management if needed. Therefore, facilities that employ midlevel prescribers already have an infrastructure in place for consultation and referral.

Reviewer's Final Recommendation:

Based on the available evidence, it is safe for midlevel providers to administer medical abortion. The term in the revised Prescriber Agreement Form will be "a healthcare provider who prescribes." Per the review by the (b) (6) ((b) (6) dated March 29, 2016, this term provides an accurate

[85] Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousieguez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ 2015;93:249-258.

representation of the varied practitioners who are prescribers, while at the same time using language that is consistent with statute. We concur with the (b) (6) review.

3. Removal of references to "Under Federal Law" from the Prescriber's Agreement

The Applicant requests removal of the phrase "under Federal law" from the Prescriber's Agreement portion of the REMS materials. The phrase appears in two places:

- "Under Federal law, Mifeprex must be provided by or under the supervision of a licensed physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately.
  - Ability to diagnose ectopic pregnancies.
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."
- "Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss them, obtain her signature on the Patient Agreement, and sign it yourself."

The Applicant rationalizes that all of the conditions of Mifeprex approval, including the REMS, are under Federal law and that the statement is redundant and are no more subject to Federal law than the other conditions of approval.

Reviewer comment:
A rationale for the original inclusion of the phrase "Under Federal law" cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and can be removed from the Prescriber's Agreement.

Reviewer's Final Recommendation:
The term "under Federal law" can be removed from the Prescriber's Agreement.

4. Addition of misoprostol to the indication statement

The Indication and Usage section of the currently approved labeling is as follows:

> "Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation

occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination.

Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 mcg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS)."

The Applicant proposed two alternative indication statements, both of which include reference to misoprostol:

(b) (4)

Or

(b) (4)

The Applicant provides the rationale that:

- the two drugs are used in combination and placing misoprostol in the indication statement early on in labeling gives it greater prominence and highlights the importance of completing the full treatment regimen

- the mention of misoprostol enhances the goal of labeling, which is to give healthcare providers information necessary for safe and effective use of Mifeprex.

Subsequently on February 25, 2016, the Applicant proposed (b) (4) (b) (4) gestational age through 70 days, based on the literature already submitted.

Reviewer comment:

We recommend that the Indication Statement read:

> **"Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation."**

The rationale for this is that:

- **All supporting data are based on the combined regimen**
- **Inclusion of misoprostol in the Indication Statement would be consistent with the rest of Mifeprex labeling and with current medical practice**
- **It would be consistent with current FDA thinking (e.g., the internal Label Review Tool) which states that the indication and use statement should include "Information if drug is to be used only in conjunction with another therapy."**

Reviewer's Final Recommendation:

Misoprostol should be included in the Indication Statement for Mifeprex.

8 Postmarket Experience

A comprehensive review of the adverse events associated with Mifeprex from September 28, 2000 through November 17, 2015, performed by (b) (6) , (b) (6), yielded the following information on reported deaths. Regarding the US cases, there were 17 reported deaths. Deaths were associated with sepsis in eight of the 17 (seven cases tested positive for *Clostridium sordellii,* one case tested positive for *Clostridium perfringens).* Seven of the eight fatal sepsis cases reported vaginal misoprostol use; one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a case of delayed onset toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. The autopsy report on the ninth death became available to the Agency and was reviewed on December 2, 2015. It showed the woman died of pulmonary emphysema.

There were 11 additional deaths in women in foreign countries who used mifepristone for medical termination of pregnancy. These fatal cases were associated with the

following: sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial; sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure;" thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes, a jejunostomy feeding tube, and severe cystic fibrosis; and a case of *Clostridium sordellii* sepsis (from a published literature report).

Reviewer Comments:

While an exact rate of death with use of mifepristone cannot be calculated from this information, given that there have been over 2.5 million uses of Mifeprex by US women since its marketing in 2000, the number of deaths is very low. Moreover, half of the deaths were associated with *C. sordellii* sepsis. Seven out of 8 of these cases occurred in women who used misoprostol via the vaginal route while one used buccal misoprostol. Since at least 2006, PPFA (comprising the majority of US medical abortion providers) switched its national guidelines to avoid vaginal administration of misoprostol (even though the data did not find a causal relationship).[23] Although the possibility that Mifeprex might increase the likelihood of infection by adversely affecting immune system function has been raised, the overall event rate of serious infections does not support this.

Since 2009, there have been no *C. sordellii* deaths associated with medical abortion in the US. This reviewer finds that the postmarketing data on deaths associated with medical abortion demonstrate low numbers and an improved safety profile with the buccal route of misoprostol administration as compared with the vaginal route.

The review by (b) (6) (b) (6) also yielded the following

Table 21 summarizing hospitalizations, blood loss requiring transfusions, and severe infections.

Table 21: US Postmarketing AEs- Mifepristone for Medical Abortion

Date ranges of reports received	09/28/00[†]-10/31/12	11/1/12 - 04/30/14[‡]
Cases with any adverse event	2740	504
Hospitalized, excluding deaths	768	110
*Experienced blood loss requiring transfusions[§]	416	66
Infections[‖] (*Severe infections[¶])	308 (57)	37 (5)

† U.S. approval date.
‡ FDA implemented FAERS on September 10, 2012, and migrated all of the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. As a result of this change, it is not recommended to calculate a cumulative number when reviewing the data provided in Table 5.
* The majority of these women are included in the hospitalized category in Table 5.
§ As stated in the approved Mifeprex (mifepristone) labeling, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days. Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.
‖ This category includes endometritis (inflammation resulting from an infection involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as chlamydia and gonorrhea, cystitis, and toxic shock syndrome not associated with a pelvic infection.
¶ This subset of infections includes cases that were determined to be severe based on medical review of the available case details. Severe infections generally result in death or hospitalization for at least 2-3 days, require intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, or have other physical or clinical findings, laboratory data, or surgery that suggest a severe infection.

Source: Review by (b) (6) (b) (6) (b) (6) dated 08/27/2015.

The (b) (6) review also describes ectopic pregnancies:

Table 22: US Postmarketing Ectopic Cases- Mifepristone for Medical Abortion

Date Range of Cumulative Reports	9/28/2000-10/31/14*	11/1/14-4/30/2015
Ectopic Pregnancies†	79	10

* U.S. approval date

† Administration of mifepristone and misoprostol is contraindicated in patients with confirmed or suspected ectopic pregnancy (a pregnancy outside the uterus).

Source: (b) (6) (b) (6) (b) (6) Mifepristone U.S. Post-marketing Adverse Events 6 month Update Summary through 04/30/2015, dated 08/20/2015.

Reviewer comment:

While exact rates cannot be calculated, as these reports are spontaneously generated, a few conclusions can be drawn from the information provided:

- **Given that there have been over 2.5 million uses of Mifeprex by US women since its marketing in 2000, including the use of the proposed dosing regimen and extended gestational age at many clinic/office sites, the numbers of hospitalizations, severe infections, blood loss requiring transfusion and ectopic pregnancy will likely remain acceptably low.**
- **The numbers of each of these adverse events appears to have remained steady over time, with a possible decrease in severe infections.**

A discussion of a (b) (6) review of uterine rupture is found in the Section Significant Adverse Events.

(b) (6) identified another safety signal in a review dated January 27, 2016. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. A literature search did not reveal any case reports of either adverse event with mifepristone. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of the various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema.

In the case of anaphylaxis, it was reported that the patient experienced an anaphylactic reaction three hours after mifepristone administration; however, co-administration of doxycycline was also documented. Because both mifepristone and doxycycline were discontinued simultaneously, the exact cause of the anaphylactic reaction cannot be determined.

Regarding angioedema, five of the six cases noted a time-to-onset within 24 hours of mifepristone administration for the termination of pregnancy, with no additional suspect medications reported. The remaining case of angioedema with mifepristone reported a time-to-onset of approximately one week in a Cushing's syndrome patient with a complex medical history and multiple concomitant medications; however, this case noted both a positive dechallenge and rechallenge upon sole re-introduction of mifepristone therapy. Evaluation of these FAERS cases provides supportive evidence of a drug-event association between angioedema and mifepristone. The (b) (6) reviewer recommends the inclusion of anaphylaxis and angioedema within the Mifeprex labeling, specifically to the Contraindications and Adverse Reactions Postmarketing Experience sections.

Reviewer Comment:

There does appear to be an association with angioedema and mifepristone administration. The reviewers agree with inclusion of anaphylaxis and angioedema in the labeling for Mifeprex and with continued pharmacovigilance for anaphylaxis.

9 Appendices

9.1 Literature Review/References

This NDA review obviously involved an extensive review of resources and the peer-reviewed medical literature that was pertinent to the requested changes of the Applicant. Such sources are noted throughout the review in footnotes. A detailed Reference List is found in Appendix 9.6.

9.2 Labeling Recommendations

The package insert (PI) for this product was submitted in the Physician Labeling Rule (PLR) format. Although not required for this supplement, Section 8 was revised in accord with the Pregnancy and Lactation Labeling Rule (PLLR). Section 17 Patient Counseling Information was also revised to be compatible with the new dosing regimen and follow-up. Major changes were made that updated the labeling with new safety and efficacy information, especially in two areas:

1) 6.1 Clinical Trials Experience in the section 6 Adverse Reactions
2) 14 Clinical Studies

Changes were also made in the patient package insert (PPI) and Medication Guide for the product. These format and content updates marked a significant improvement in the label. Agreement on the Final Approved label was reached with the Applicant on March 29, 2016.

Reviewer comment:

The new dosing regimen was based on the extensive number of articles submitted by the Applicant from the peer reviewed medical literature. The revised label used the new PLR format which is a complete change from the previous style. This meant that the newly approved label was extensively rewritten and much improved from the old format.

9.3 Advisory Committee Meeting

An Advisory Committee met in 1996 to discuss the approval of mifepristone plus misoprostol for medical termination of early pregnancy. There has been extensive US (15+ years with over 2.5 million uses) and global use (27+ years) of mifepristone and misoprostol for the medical termination of early pregnancy. No special external consultations were requested by the review Divisions. The FDA determined that the efficacy supplement did not raise complex scientific or other issues that would warrant holding an advisory committee meeting before approval of the supplement.

9.4 (b) (6) ((b) (6) Meeting

As noted in Product Regulatory Information, Mifeprex was originally approved under 21 CFR part 314, subpart H, “Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses” (subpart H). Specifically, in accordance with § 314.520 of subpart H, FDA restricted the distribution of Mifeprex and required that Mifeprex be provided by or under the supervision of a physician who met certain qualifications. Further, practitioners had to complete a Prescriber’s Agreement, provide patients with a Medication Guide and have patients sign a Patient Agreement. Mifeprex was included on the list of products deemed to have in effect an approved REMS[86] under section

86 Federal Register / Vol. 73, No. 60 | Issued: March 27, 2008

505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of FDA Amendments Act (FDAAA) of 2007. A formal REMS proposal was submitted by Danco and approved on June 8, 2011, with the essential elements unchanged. The REMS included:

- Medication Guide
- Elements to Assure Safe Use (ETASU):
  - Prescribed only by certified prescribers (ETASU A; includes a Prescriber's Agreement)
  - Dispensed only in certain healthcare settings (ETASU C)
  - Dispensed with documentation of safe use conditions (ETASU D; includes a Patient Agreement)
- Implementation System
  - Distributed only by certified distributors

Following this approval, two REMS assessment reports were completed. The Year 1 assessment was completed on June 1, 2012 and the Years 2-4 assessment was completed on June 2, 2015. Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

On July 16, 2015, the Applicant submitted a revised REMS as part of the efficacy supplement. The proposed modifications included:

- Prescriber's Agreement Form
  - Remove "Under Federal law"
  - Replace "physician" with "(b) (4)

The Agency determined that broader review of the REMS was warranted concurrently with the efficacy supplement because some proposed changes in labeling dovetail with proposed changes to the REMS, and the documents should remain consistent with each other. Further, extensive review of the postmarketing experience based on the literature submitted to support the efficacy supplement, and pharmacovigilance, suggested that certain components of the REMS may no longer be necessary to assure safe use of Mifeprex.

In light of the efficacy review, upon assessment of the proposed modifications, (b) (6) concurs with (b) (6) recommendations that:

- Removal of "under Federal law" from the Prescribers' Agreement was acceptable (see discussion in Additional Submissions / Issues)
- The term "healthcare providers who prescribe" is preferable to (b) (4) (see discussion in Additional Submissions / Issues)

(b) (6) and (b) (6) also proposed the following modifications:

- Removal of the Medication Guide from the REMS (will remain a part of labeling and must be distributed by the prescriber as required under 21 CFR part 208)
- Removal of the Patient Agreement form - Documentation of Safe Use (ETASU D)

- Revision of the Prescriber's Agreement form
- Revision of the REMS goal to reflect above changes

FDA considered the need for the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." FDA has received such reports for 15 years; the safety profile of Mifeprex is well-characterized, no new safety concerns have arisen in recent years, and the known serious risks occur rarely. For this reason, the reviewers do not believe ongoing reporting of all of the specified adverse events is warranted. The Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience.

(b) (6) and (b) (6) met with the (b) (6) ((b) (6) on January 15, 2015, to discuss the proposed modifications. The (b) (6) concurred with the removal of the term "under Federal law" and with use of the term "healthcare providers who prescribe." The (b) (6) also concurred with the removal of the Medication Guide (MG) from the REMS, though the document would remain a part of labeling. FDA has been maintaining MGs as labeling but removing them from REMS when, as here, inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks, such as when the MG is redundant and not providing additional use or information to the patient about the risk(s) the REMS is intended to mitigate. This is consistent with ongoing efforts to streamline REMS by allowing for updates to the MG without need for a REMS modification. (b) (6) and the (b) (6) had subsequent interactions and on February 23, 2016, the (b) (6) concurred with the decision to remove the Patient Agreement (ETASU D) from the REMS. This decision was based on the following rationale:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance
- Established clinical practice includes patient counseling and documentation of Informed Consent, and, more specifically with Mifeprex, includes counseling an all options for termination of pregnancy, access to pain management and emergency services if needed. The National Abortion Federation (NAF) provides clinical practice guidelines**Error! Bookmark not defined.** and evidence shows that practitioners are providing appropriate patient counseling and education; a survey published in 2009 demonstrated that 99% of facilities surveyed provided pre-abortion counseling with patient education.[87] This indicates that the Patient Agreement form is duplicative and no longer necessary to ensure that the benefits of the drug outweigh the risks.

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[87] O'Connell K, Jones HE, Simon M, Saporta V, Paul M, Lichtenberg ES. First-trimester surgical abortion practices: a survey of National Abortion Federation members. Contraception 2009; 79: 385–392.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines cover the safety information that is duplicated in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the supervision of a certified prescriber at the time the patient receives treatment with Mifeprex.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

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9.4 Abbreviations

List of Abbreviations

Abbreviation	Term
ACOG	American College of Obstetrics and Gynecology
APHA	American Public Health Association
CDER	Center for Drug Evaluable and Research
CDRH	Center for Devices and Radiological Health
(b) (6)	(b) (6)
FU	follow up
GA	gestational age
IRB	Institutional Review Board
LFU	lost to follow up
LMP	last menstrual period
MAB	medical abortion
MG	Medication Guide
Miso	misoprostol
NA	not applicable
NAF	National Abortion Federation
NDA	New drug application
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
PPFA	Planned Parenthood Federation of America
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategies
ROA	route of administration
(b) (6)	(b) (6)
SAB	surgical abortion
WHO	World Health Organization

9.5 List of References

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9.6 Mifepristone Approvals Globally

1988
- China
- France

1991-
- UK

1992
- Sweden

1999
- Austria
- Belgium
- Denmark
- Finland
- Germany
- Greece
- Iceland
- Israel
- Luxembourg
- Netherlands
- Russia
- Spain
- Switzerland

2000
- Norway
- Taiwan
- Tunisia
- US

2001
- New Zealand
- South Africa
- Ukraine

2002
- Belarus
- Georgia
- India
- Latvia
- Serbia
- Vietnam

2003
- **Estonia**

2004
- Guyana
- Moldova

2005
- Albania
- Hungary
- Mongolia
- Uzbekistan

2006
- Kazakhstan

2007
- Armenia
- Kyrgyzstan
- Portugal
- Tajikistan

2008
- Nepal
- Romania

2009
- Cambodia
- Italy

2010
- Zambia

2011
- Ghana
- Mexico
- Mozambique

2012
- Australia
- Bangladesh
- Ethiopia
- Kenya

2013
- Azerbaijan
- Bulgaria
- Czech Republic
- Slovenia
- Uganda
- Uruguay

2014
- Thailand

2015
- Canada

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

(b) (6)

03/29/2016

(b) (6)

03/29/2016

I concur with (b) (6) conclusions and recommendations for approval of this efficacy supplement.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 020687 **Applicant: Danco Labs** **Stamp Date: May 29, 2015**

Drug Name: Mifeprex (Mifepristone) **NDA/BLA Type: supplement #020**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			Paper submission.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?			x	
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?		x		The applicant has not provided module 2 summaries as this is an NDA based on published literature. The applicant has provided a justification summarizing the evidence of safety and efficacy for the proposed changes.
9.	Has the applicant submitted the integrated summary of safety (ISS)?		x		See comment for 8.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		x		See comment for 8.
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Scientific justification-30 pg document
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	x			(b) (2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	x			The sponsor provides a bridge from the approved product to the proposed changes, with literature based

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					on both the approved product and the proposed regimen.
15.	Describe the scientific bridge (e.g., BA/BE studies)	x			See #14.
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Many articles from the published medical literature. Study Title: Sample Size: Arms: Location in submission:	x			
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:	x			The applicant provides 54 articles total, with 32 specifically on efficacy of the proposed regimen. These include controlled trials, meta-analyses, observational and retrospective studies.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	The applicant provides 54 articles total. 46 are studies (trials, retrospective, observational studies) and of these 17 are foreign. There are also 3 metanalyses which include foreign studies.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			The applicant provides 21 articles with information on safety, specifically on the serious adverse events of interest (hospitalization,

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					transfusion, infection requiring IV antibiotics, death). There are another 5 articles with limited safety information and 6 articles with safety information, but using different dosing regimens (e.g. not the approved or proposed new regimen).
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			x	There is no mapping of investigator terms to preferred terms. AE's were variably ascertained; 21 studies include data on SAE's of interest, 7 have limited safety information, 6 have safety information on the approved dosing regimen. Some 7 studies report no safety information.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	As of 7/16/15, there is one reported death; a complete report will be forthcoming. This

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					is not part of the presently submitted application.
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			The applicant requested a partial waiver for patients <12 and a waiver for patients 12-17, based on data from one study which included 322 subjects <17 years old.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	29/46 studies are US data, 17 are based on foreign data.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	NDA relies upon published studies; datasets were not provided.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
37.	Are all datasets to support the critical safety analyses available and complete?			x	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	NDA relies upon published studies; CRFs were not provided.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an			x	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There is one review issue which will need to be addressed.
The proposed label contains information from the original studies and not from the studies supporting the new dosing regimen and the other proposed changes (e.g., including healthcare providers prescribing Mifeprex and home use of misoprostol). The Sponsor will need to update the proposed label.

(b) (6) 7/16/15

Reviewing Medical Officers Date

(b) (6) 7/16/15

Date

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/s/

(b) (6)

07/16/2015

(b) (6)

07/17/2015

(b) (6)

07/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-020

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated July 17, 2015.

This "Prior Approval" supplemental new drug application proposes to provide for use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because the use of this product before menarche is not indicated, and we have determined that you have fulfilled the pediatric study requirement for post-menarcheal patients.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The REMS consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS included revisions to both the prescriber and patient agreement forms.

Other changes proposed in the efficacy supplement prompted additional revisions to the Mifeprex REMS materials. During review of this efficacy supplement, we also assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks.

After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS. The REMS modifications submitted by you on March 29, 2016 are approved.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Mifeprex outweigh its risks. The

Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on July 17, 2015, and appended to this letter, is approved as amended. The modified REMS consists of elements to assure safe use (A, C and D), an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on June 8, 2011.

The REMS assessment plan will include the information submitted to FDA on March 29, 2016.

The revised REMS assessment plan must include, but is not limited to, the following:

REMS Assessment Plan

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative).
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6) .

Sincerely,

{See appended electronic signature page}

(b) (6)
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 29, 2016
Subject	Summary Review
NDA #/Supplement #	20687/S-020
Applicant name	Danco Laboratories, LLC
Date of submission	May 28, 2015
Date of submission receipt	May 29, 2015
PDUFA goal date	March 29, 2016
Proprietary name/established name	Mifeprex/mifepristone
Dosage form/strength	Oral tablet/200 mg
Dosage regimen	Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol
Proposed indication	Mifeprex is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation
Action	Approval

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

Danco Laboratories, LLC, referred to hereafter as the Applicant, submitted an efficacy supplement (S-020) to NDA 20687 for Mifeprex (mifepristone). The Applicant sought the following changes to its approved application:

1. (b) (4) Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally; see below:
   - Day One: Mifeprex Administration (oral)
     One 200 mg tablet of Mifeprex is taken in a single oral dose
   - After a 24-48 hour interval: Misoprostol Administration (buccal)(minimum 24-hour interval between Mifeprex and misoprostol)
     Four 200 mcg tablets (total dose: 800 mcg) of misoprostol are taken by the buccal route

2. Removal of the instruction that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex
5. Increase in the maximum gestational age from 49 days to 70 days
6. Change of the labeled time for expected expulsion of pregnancy from 4-24 hours to 2-24 hours post misoprostol administration
7. Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change of "physician" to "healthcare provider" in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change in the indication statement to add reference to use of misoprostol: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation."
10. Removal of references to "under Federal law" from the Prescriber's Agreement under the REMS

11. Labeling changes addressing the pediatric requirements under the Pediatric Research Equity Act

This efficacy supplement submission includes information from published studies, review articles and additional information from the authors of some of the publications. These published studies evaluated reproductive age women in the U.S. and outside the U.S. who had early medical termination with mifepristone, in a regimen with misoprostol, including women up through 70 days of gestation.

This memorandum serves as the Division's decisional memorandum for the efficacy supplement.

2. Background

The active ingredient of Mifeprex, mifepristone, is a progestin antagonist. Mifeprex, in a regimen with misoprostol, is approved for the medical termination of pregnancy up through 49 days' gestation. The approved dosing regimen is currently labeled as follows:

- Day 1: The patient takes three 200 mg tablets of Mifeprex in a single oral dose in the clinic, medical office, or hospital.
- Day 3: The patient returns to the clinic, medical office, or hospital and takes two 200 mcg tablets of misoprostol orally.
- Day 14: The patient returns for a follow-up visit to confirm that a complete termination has occurred.

At the time of the September, 2000 approval, FDA restricted distribution of Mifeprex under 21 CFR 314.520, requiring that Mifeprex be dispensed only by or under the supervision of a physician who meets certain qualifications. With the passage of FDAAA in 2007, Mifeprex was deemed to have in effect an approved REMS. The Applicant submitted a formal REMS, which was approved on June 8, 2011 and consisted of the following: a Medication Guide, elements to assure safe use (ETASU A [special certification of healthcare providers who prescribe Mifeprex], ETASU C [dispensing only in certain healthcare settings], and ETASU D [safe use condition of a signed Patient Agreement]), an implementation system and a timetable for assessments. The goals of the REMS were 1) To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and 2) To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications. The REMS for Mifeprex incorporated the restrictions under which the drug was originally approved.

Since 2011, the Applicant has submitted two REMS assessment reports. The Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

FDA held a pre-NDA meeting with the Applicant on January 29, 2015, to discuss proposed labeling and REMS changes to be submitted in this efficacy supplement. These changes were submitted with the efficacy supplement.

The Applicant submitted published literature and supportive information to support changes to the dose, dosing regimen, gestational age, revisions to labeling, modifications to the REMS document, and to address PREA requirements. The Agency accepts the use of peer reviewed literature as primary data for an application under the framework of a 505(b)(2) application.

3. CMC

No new CMC information was submitted with this efficacy supplement. The CMC team determined no additional review or inspections were required. The CMC team completed a review of the labeling and found the CMC sections of labeling (sections 3, 11 and 16) acceptable (See review dated March 29, 2016). The CMC review team recommends approval of the efficacy supplement; refer also to the CMC review of the separate supplement proposing a single tablet blister pack for Mifeprex, dated January 11, 2016. There are no outstanding CMC issues or postmarketing commitments or requirements.

***Comment**: On March 10, 2016, a separate CMC supplement was approved that allowed the packaging of individual 200 mg tablets of mifepristone; previously packaging consisted of three 200 mg tablets per blister pack (a total of 600 mg Mifeprex as administered under the originally approved dosing regimen).*

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in this supplement. The Pharmacology/Toxicology team revised labeling to conform to the Pregnancy and Lactation Labeling Rule. There are no outstanding nonclinical issues. The Pharmacology/Toxicology review team recommends approval of the efficacy supplement; refer to the Pharmacology/Toxicology review dated March 4, 2016.

5. Clinical Pharmacology

The Applicant did not conduct any new clinical pharmacology studies pertaining to the proposed (b) (4) regimen, but provided information on pharmacokinetics (PK) of misoprostol following various routes of administration. The PK of the 200 mg Mifeprex tablet has not been characterized in women, but data are available in men and were submitted in the original NDA. The Clinical Pharmacology review team determined that the PK data were appropriate for inclusion in labeling. Review of the labeling pertinent to the Clinical Pharmacology sections is complete and labeling relevant to pharmacokinetics and pharmacodynamics is acceptable. There are no outstanding Clinical Pharmacology issues or postmarketing commitments or requirements. The clinical pharmacology review team recommends approval of the efficacy supplement; refer to the Clinical Pharmacology review dated March 29, 2016.

6. Clinical Microbiology

Not applicable.

7. Efficacy/Statistics

The Applicant submitted published literature as the primary evidence to support the efficacy (and safety) of the proposed dosing regimen (refer to the Clinical Review dated March 29, 2016, Section 9.5 for a list of submitted references). Most published articles submitted by the Applicant and reviewed by the clinical review team reported the primary efficacy endpoint as complete termination of pregnancy without further medical or surgical intervention; the Division considers this to be a clinically relevant endpoint.

The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent. The clinical review team concluded that the published literature was adequate as the primary information source to support the changes proposed in the efficacy supplement. During the course of the review, the team also requested and received more detailed information from select publications from their authors via communication with the Applicant.

Although there were slight demographic differences among the published studies from the database, these differences were not expected to alter the efficacy or safety of Mifeprex. Therefore, for the majority of the proposed efficacy changes, the clinical team assessed efficacy information from a subset of publications that evaluated a given proposed change. An independent statistical review was not needed for this review of published literature.

The clinical review team identified several major proposed clinical changes in the efficacy supplement. As these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes. These major changes as considered by the clinical team included:

1. A proposed dosing regimen consisting of mifepristone 200 mg orally followed by the buccal administration of 800 mcg misoprostol including:
    a. Use of a revised interval between mifepristone and misoprostol from 48 hours to 24-48 hours
    b. Allowing home administration of misoprostol
    c. Use of an additional dose of misoprostol
2. Support for extending the gestation age through 70 days
3. Flexibility in follow-up visit: follow-up is needed in the range of 7-14 days after Mifeprex administration; the specific nature and exact timing of the follow-up to be agreed upon by the healthcare provider and patient.
4. Change in who can provide Mifeprex from physician to healthcare provider who prescribes

The following section summarizes the clinical review team's evaluations that supported the above proposed changes:

1. *Support for the proposed dose and dosing regimen of 200 mg of Mifeprex orally and 800 mcg of misoprostol buccally 24-48 hours after Mifeprex administration:* The clinical review team reviewed the submission and identified studies and review articles that evaluated over 35,000 women who were treated with efficacy in the 91-98% range. For additional details on the efficacy from these studies, please refer to Section 6 of the Clinical Review.

2. *Support for extending the gestational age to 70 days:*
   The Applicant submitted a number of published articles and systematic reviews that supported the proposed dose and dosing regimen. Four studies and one systematic review evaluated the exact proposed dosing regimen through 70 days gestation. These include three prospective observational studies (Winikoff et al 2012[1], Boersma et al[2] , Sanhueza Smith et al[3]) and one randomized controlled trial (RCT) (Olavarrieta et al[4]) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin[5] covered 20 studies including over 30,000 women; all but one of the studies used the proposed regimen in gestations through 70 days (the remaining study used 400 mcg of buccal misoprostol). For those publications that provided overall success rates, these were in the range of 97-98%. Other relevant publications include the systematic review by Raymond[6] of 87 studies, which covered a variety of misoprostol doses and routes of administration used with 200 mg of mifepristone. Assessing the efficacy by misoprostol dose, the paper noted that doses ≥ 800 mcg had a success rate of 96.8%, with an ongoing pregnancy rate of 0.7%.

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[1] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6

[2] Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011; 16: 61-6

[3] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015; 22: 75-82

[4] Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousieguez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ 2015; 93: 249-258

[5] Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015; 126(1): 12-21

[6] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

The original dosing regimen specifies taking misoprostol 2 days after Mifeprex. This efficacy supplement proposes a more flexible time frame of 24 to 48 hours between Mifeprex and misoprostol administration. Data from a review article by Wedisinghe et al[7] evaluated different time intervals using administration of misoprostol after Mifeprex. A meta-analysis of all five studies found a non-significant odds ratio for failure for shorter vs. longer dosing intervals, but a trend for lower success if a dosing interval < 8 hours is used. Chen & Creinin's systematic review[8] of 20 studies including over 33,000 women, all but one using the proposed regimen, compared the success of dosing intervals of 24 hours with intervals ranging from 24-48 hours. The success rate in six studies that used a 24-hour interval through 63 days gestation was 94.2%, compared to the rate of 96.8% in 14 studies that used a 24-48 hour interval, and this difference was statistically significant. The clinical team concluded that the efficacy of the revised dosing regimen was not compromised by revising the dosing interval to 24-48 hours. In addition, they noted that the overall rate of ongoing pregnancies did not differ significantly by dosing interval.

3. *Administration of misoprostol after Mifeprex administration at home:* Currently, the dosing regimen specifies that misoprostol is taken in the clinic setting following Mifeprex administration. No specific publication evaluated treatment outcomes with use of misoprostol at home compared to in-clinic dosing. However, one large literature review (Raymond et al[9]) evaluated a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration and dosing intervals used in gestations through 63 days. Roughly half of the studies included in this review did not require women to take misoprostol in-clinic. Rates of treatment failure and of ongoing pregnancy were very similar regardless of whether misoprostol was taken in-clinic or at another location. The clinical review team concluded that the review provided sufficient data to support labeling that misoprostol does not need to be restricted to in-clinic administration.

4. *Use of a repeat misoprostol dose, if necessary:* The Applicant submitted several published studies that supported use of a repeat misoprostol dose, when complete uterine expulsion did not occur after the initial misoprostol dose following Mifeprex. In clinical practice, the usual treatment for incomplete expulsion (retained products of conception) may include either a repeat dose of misoprostol, expectant management or a surgical procedure (suction aspiration or a dilation and curettage). Studies that specifically report the success rate of a repeat dose of misoprostol are:

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[7] Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. Contraception 2010; 81(4): 269-74. doi: 10.1016/ j.contraception.2009.09.007. Epub Oct 29, 2009

[8] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859

[9] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

- Winikoff et al[10] – studied the proposed regimen through 70 days gestation; of the few women who received a second dose for an incomplete abortion at follow-up, the success rate was 91% at 57-63 days and 67% at 64-70 days.
- Chen and Creinin [11] – a systematic review of 20 studies, all but one of which used the proposed regimen up through 70 days; success of a second dose ranged from 91-100%
- Boersma et al[12] – included pregnancies through 70 days treated with the proposed regimen; five of 330 women took a second dose due to absence of bleeding 48 hours after first dose; the success rate was 80%
- Louie et al[13] – studied the proposed regimen to 63 days; in 16 women (of 863) who took a second dose of misoprostol, the success rate was 100%
- Chong et al[14] – compared the proposed regimen to a lower dose of misoprostol; the success of a second dose of misoprostol was 92% overall, but the number of women in each dose arm getting a second dose was not specified.
- Winikoff et al[15] – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%.

Using the information from the above studies and other supportive data, the clinical team concluded that the available data support the efficacy of a repeat dose of misoprostol if complete expulsion has not occurred. The relatively high complete pregnancy termination rates indicate that this option is likely to reduce the need for a surgical intervention.

5. *Requirements regarding follow-up care:* Current labeling states that women will return to the clinic 14 days after Mifeprex administration for follow-up. This provision was based on the follow up regimen in the U.S. phase 3 trial that supported the initial approval in 2000. Although the Applicant submitted several studies that evaluated flexibility in the time of follow-up, the key publication identified by the review team that addressed this issue was a 2013 article by

[10] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6
[11] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859
[12]Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011; 16: 61-6
[13] Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. Eur J Contracept Reprod Health Care 2014; 19(6): 457-464
[14] Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. Contraception 2012; 86: 251-256
[15] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008; 112(6): 1303-1310

Raymond[16]. The impact of the timing of follow-up was assessed in Raymond's systematic review of studies using various treatment regimens. While some have posited that earlier follow-up may result in a higher rate of surgical intervention (for women who would have had complete expulsion had they been given a bit more time), Raymond's analyses found no difference in failure rates for women followed less than one week after mifepristone as compared to a week or more after mifepristone. As follow-up was anticipated to not alter the efficacy of the proposing dosing regimen, this change is also discussed below in Section 7.

6. *Allowing qualified healthcare providers to use Mifeprex.*

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies included a study by Warriner et al[17] that showed efficacy of 97.4% with nurses versus 96.3% by physicians.

Conclusions: I concur with the clinical review team's assessments and conclusions and these conclusions will be reflected in labeling. The data and information reviewed constitute substantial evidence of efficacy to support the proposed dosing regimen for Mifeprex for pregnancy termination through 70 days gestation. Other proposed changes to the Mifeprex labeling, including the time interval between Mifeprex and misoprostol dosing, and use of a repeat dose, were also adequately supported by evidence. Finally, I concur with the clinical review team that the information from the published literature also supported efficacious use of Mifeprex by non-physician providers.

Comment: Discussion was held as to whether the original dosing regimen approved in 2000 (i.e., Mifeprex 600 mg and misoprostol 400 mcg up to 49 days gestation) should remain in labeling. (b) (4) the clinical review team and I concur with their (b) (4) request to remove the current regimen from the labeling. Removal of the original dosing regimen simplifies labeling, and avoids any confusion regarding instructions. Therefore, the revised labeling, and REMS materials accompanying the approval of this efficacy supplement, will include only the proposed dosing regimen and instructions. It should be noted that there are no safety or efficacy concerns about the originally approved dosing regimen that led to removing it from the labeling.

[16]Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.

[17] Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-61.

8. Safety

The safety of the proposed dosing regimen for Mifeprex was supported by the evidence from submitted published literature and postmarketing experience. The focus of the safety analysis was on published studies that evaluated the proposed dosing regimen (Mifeprex 200 mg followed by 800 mcg misoprostol buccally 24-48 hours later), with comparison to the known safety profile of the currently approved dosing regimen.

Exposure: Per the Applicant's submission, the clinical review concluded that there have been approximately 2.5 million uses of Mifeprex by U.S. women since the drug's approval in 2000. The clinical review team estimated that exposure to the proposed dosing regimen for their safety analysis was based on approximately 30,000 patients (refer to Table 11 for a list of references used to evaluate safety). Such exposure volume is sufficient to characterize the safety profile of the proposed dosing regimen and other proposed changes in this efficacy supplement.

Deaths: Deaths with medical abortion rarely occur and causality can be difficult to determine. Most of the publications did not specifically report any deaths with medical abortion with Mifeprex. Among the seven U.S. studies submitted to support the safety profile of Mifeprex and misoprostol, only one (Grossman, et al[18]) explicitly addressed deaths and noted that there were no deaths among 578 subjects evaluated in the study. Only one observational study (Goldstone, et al[19]) from Australia contained a report of a death after a mifepristone and misoprostol dosing regimen. In this retrospective review of 13,345 pregnancy terminations, the authors identified one death from sepsis. The article stated that the death was in an individual who failed to follow-up with her healthcare provider despite showing signs of illness. Based on this information, deaths in association with abortion are extremely rare.

Deaths reported from the postmarketing experience of Mifeprex are summarized below in the Postmarketing Experience section.

Nonfatal serious adverse events: The clinical review team identified key nonfatal serious adverse events (SAEs) associated with the proposed dosing regimen for Mifeprex. These SAEs include: hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. Section 7 of the clinical review dated March 29, 2016, provides a detailed discussion of reported rates of hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. The latter is not an adverse reaction because an ectopic pregnancy would exist prior to the Mifeprex regimen; it represents instead a failure to diagnose an ectopic pregnancy. Overall rates identified by the clinical review team from the published literature are as follows:

- Hospitalization: 0.04-0.6% in U.S. studies of over 14,000 women; 0-0.7% in international studies of over 1,200 women

[18]Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.
[19]Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. Med J Austral 2012; 197: 282-6.

- Serious infection/sepsis: 0-0.2% in U.S. and international studies of over 12,000 women
- Transfusion: 0.03-0.5% in U.S. studies of over 17,000 women; 0-0.1% in international studies of over 12,000 women

A study by Upadhyay et al[20] reported a 0.31% rate of major complications (including incomplete or failed abortion, hemorrhage, infection or uterine perforation that required hospitalization, surgery or transfusion) for medical abortions (dosing regimen unspecified) through 63 days; this was about double the rate reported for first trimester aspiration abortions and statistically significantly higher. However, these rates were driven by higher rates of incomplete/failed abortion; rates of hemorrhage (0.14%) and infection (0.23%) did not differ from those associated with aspirations.

Only one submitted study reported an ectopic pregnancy. This study (Winikoff et al[21]) reported one ectopic among 847 women (0.12%).

Comment: The proposed dosing regimen has been studied extensively in the literature using U.S. and global sites. Serious adverse events including deaths, hospitalization, serious infections, bleeding requiring transfusion and ectopic pregnancy are rarely reported. The rates of these serious adverse events are well below 1% and do not suggest a safety profile different from the original approved Mifeprex dosing regimen. Although there is less serious adverse event data on women who received Mifeprex and misoprostol between 64-70 days of gestation, the data from a U.S. study of 379 women (Winikoff et al)[22] in that gestational age is reassuring that the rates of these serious adverse events are not clinically different from that of other gestational age ranges.

In summary, based on the published literature, nonfatal serious adverse events occur with Mifeprex and misoprostol use with rates generally less than 1%. Increased gestational age (64-70 weeks) was not associated with an increased incidence of nonfatal SAEs. Other submission- specific safety issues that were evaluated including uterine rupture and angioedema/anaphylaxis are discussed in the Postmarketing Experience section below.

Loss to follow-up: The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc et al[23]) to 22% in the Grossman et al[24] study using telemedicine to deliver medical

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[20]Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. Obstet Gynecol 2015;125(1):175-183.
[21]Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008;112(6):1303-1310.
[22]Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012;120:1070-6.
[23] Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. Obstet Gynecol 2014;123:88-95.
[24] Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.

abortion services.

Comment: Based on these data reviewed by the clinical review team, there is no literature that suggests that follow-up modality alters safety. Therefore, labeling will not be directive regarding follow-up; that will be a decision left to the patient and provider.

Common adverse events: The clinical review team evaluated common adverse reaction data and compared U.S. and global study locations. The comparison revealed that there were differences in the frequency of common adverse reactions, with the reporting rates considerably higher among the U.S. studies. There is no reason to anticipate regional differences in the safety profile for the same treatment regimen, so these differences likely reflect lower ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data in labeling would not be appropriate, as it is unlikely to be informative to the U.S. population of users. The data to be reported in labeling is outlined in Table 1 below:

Table 1: Common Adverse Events (≥ 15%) in U.S. Studies of the Proposed Dosing Regimen

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

Source: Data from Middleton[25], Winikoff[26] and Winikoff[27] as outlined in Table 2 of the CDTL review dated March 29, 2016.

One concerning adverse event is severe vaginal bleeding. Severe vaginal bleeding can result in interventions such as hospitalization and transfusion and may be associated with infection. The overall rate of bleeding across publications varied between 0.5% and 4.2%. Two publications (Sanhueza Smith et al[28] and Gatter et al[29]) evaluated clinically significant bleeding by gestational age. Although the publications reported slightly different rates, there was no trend of increased bleeding requiring intervention with Mifeprex and misoprostol use with increasing gestational age.

[25] Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005; 72: 328-32

[26] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6

[27] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008; 112(6): 1303-1310

[28] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015;22:75-82.

[29] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.

Comment: While not all of the studies reported common adverse events, those that reported did not have unexpected rates of common adverse events. These common adverse events are included in labeling in section 6.1 (Clinical Trial Experience) in the ADVERSE REACTIONS section.

Postmarketing experience – Spontaneous reports:

The safety profile for Mifeprex includes over 15 years of postmarketing safety data available on Mifeprex due to the reporting requirements under the REMS. The Year 3 REMS Assessment report was submitted by the Applicant in June, 2015. The (b) (6) (b) (6) provided a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. Findings include:

- No Clostridial septic deaths reported in the U.S. since 2009, and none worldwide since 2010.
- The postmarketing rates of hospitalization, severe infection, blood loss requiring transfusion and ectopic pregnancy reported from publications and remain stable and relatively low.

Submission-specific safety issues:

- Anaphylaxis/angioedema: The (b) (6) ((b) (6) identified a safety signal of anaphylaxis and angioedema with mifepristone administration. This signal was based on a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema. There were no additional cases of anaphylaxis or angioedema identified in the literature.

  Comment: (b) (6) and the clinical review team recommended that anaphylaxis and angioedema be described in the Contraindications and Adverse Reactions sections of labeling. These labeling sections were discussed with the Applicant and labeling was revised for those sections to describe these serious adverse events.

- Uterine rupture: As discussed in the clinical review, the potential risk of uterine rupture was considered because the current labeling for misoprostol includes a Boxed Warning against the use of misoprostol for gestations more than 8 weeks due to the risk of uterine rupture. Although misoprostol is used alone for various obstetric indications, including induction of labor at term, it was important to consider whether labeling about this potential risk is warranted for Mifeprex. Both the clinical reviewer and the (b) (6) ((b) (6) reviewed the literature and (b) (6) searched FAERS for adverse event reports.

Published literature reported three case reports[30,31,32] of uterine rupture with mifepristone/misoprostol treatment in the first trimester. Of these three reports, two patients had a risk factor for uterine rupture (prior uterine surgery). The third case was in a patient who received more than two doses of misoprostol. After consideration, the clinical review team decided that labeling should include information about this event. The FAERS search did not identify any reports of uterine rupture with use of mifepristone alone. Of 80 reports, 77 cited use of misoprostol alone, and three of mifepristone and misoprostol. Only two reports of uterine rupture in the first trimester were identified, both using misoprostol alone; one entailed an unspecified dose and route of misoprostol at 5 weeks gestation, and one involved vaginal administration of 800 mcg misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar.

Based on the available safety reports of uterine rupture, the review team from (b) (6) and clinical review team concluded that these data demonstrated that uterine rupture with Mifeprex and misoprostol in the first ten weeks (70 days) of gestation is exceedingly uncommon, and occurs most often in the face of a risk factor (previous uterine surgery).

Comment: I agree with the clinical review team and the (b) (6) team that the risk of uterine rupture with first trimester use of mifepristone and misoprostol appears to be extremely rare, and most often associated with a prior uterine scar, a known risk factor for uterine rupture. Labeling of these reports is included in section 2.3 of the DOSAGE AND ADMINISTRATION and section 6.2 of the ADVERSE REACTIONS of labeling to provide additional information to healthcare providers, but no restriction of use is needed based upon this extremely rare adverse reaction.

The clinical review team also evaluated the safety for each of the following major changes proposed in this efficacy supplement:

1. Changing the dosing interval between Mifeprex and misoprostol from 48 hours to 24-48 hours
2. Home administration of misoprostol
3. Use of a repeat dose of misoprostol
4. Change in the follow-up timeframe and method of follow-up
5. Allowing providers other than physicians to provide Mifeprex

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[30] Khan S et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. Journal of Obstet Gynaecol 2007; 27: 869-870

[31] Bika O, Huned D, Jha S, Selby K Uterine rupture following termination of pregnancy in a scarred uterus J Obstet Gynaecol 2014; 34(2): 198-9. doi: 10.3109/01443615.2013.841132

[32] Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. BJOG 2008;15:575-77

To evaluate each of these changes, the reviewers evaluated the adverse event information regarding:

- *Changing the timing interval between Mifeprex and misoprostol and change in the gestational age to 70 days:* Support for the 24-48 hour interval and use up through 70 days was primarily based on a large systematic review by Shaw et al[33]. This review evaluated studies looking at different follow-up modalities and demonstrated that there are a variety of acceptable alternatives to in-clinic follow-up that can identify cases in which there is need for additional intervention. In addition, the systematic review did not identify any significant difference in adverse events with different time intervals. Based on these findings, labeling will not be directive regarding specific details of how follow-up should be performed; this will be a decision between the patient and her healthcare provider.

- *Home administration of misoprostol:* The Applicant supplied several published studies that supported this change including Gatter et al[34] and Ireland et al[35]. These studies reported on large numbers of women in the U.S. who took misoprostol at home. The authors showed that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the studies of clinic administration of misoprostol that supported the initial approval in 2000. Given that information is available on approximately 45,000 women from the published literature, half of which incorporated home use of misoprostol, there is no clinical reason to restrict the location in which misoprostol may be taken. Given the fact that the onset of cramping and bleeding occurs rapidly (i.e., generally within 2 hours) after misoprostol dosing, allowing dosing at home increases the chance that the woman will be in an appropriate and safe location when the process begins.

- *Use of a repeat dose of misoprostol:* Safety reporting from studies that evaluated a repeat dose of misoprostol did not specifically assess the subset of women who received a second dose, but no unexpected findings were identified. One randomized controlled trial (Coyaji et al[36]) conducted in 300 women seeking medical abortion in India looked at a single misoprostol dose as compared to two misoprostol doses. Although there was no difference in the complete pregnancy termination rate in women who received a second misoprostol dose compared to those who did not, the repeat misoprostol dose reduced the need for surgical intervention. This study was reassuring in that there was no significant difference in the adverse events observed—similar percentages of women experienced

[33] Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. Obstet Gynecol 2013;121(6):1335-1347.
[34] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[35] Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. Obstet Gynecol 2015;126:22-8.
[36] Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? BJOG 2007;114:271-278.

cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). A supportive systematic review by Gallo et al[37] also provided safety information on subjects who received repeat misoprostol. In this review, the only side effects discussed in the trials were diarrhea, which was more common on those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported <1%. Based on these findings, labeling will be changed because the misoprostol dose does not need to be restricted to in clinic administration to assure safe pregnancy termination using the proposed dosing regimen. Given the onset of bleeding and cramping after misoprostol, allowing home administration increases the likelihood that a woman will be in an appropriate and safe location when the pregnancy termination process begins.

- *Change in the follow-up timeframe and method of follow-up:* The Applicant submitted several articles that described different methodologies in follow-up including phone calls and standardized instructions. The clinical reviewers evaluated a study in Scotland by Cameron et al[38] that evaluated self-assessment as compared to standard follow-up methodologies (clinic visit or phone call). Most of the women chose self-assessment over an in-clinic visit or phone call, and there were no significant differences in adverse outcomes between women who underwent self-assessment of health compared to those who had a clinic visit or phone call. Among women with an ongoing pregnancy after Mifeprex and misoprostol, the majority self-identified and presented within two-weeks for care. Based on this information and the other data from the Raymond systematic article[39] that did not identify a difference in failure rate for earlier (less than one week) as compared to one week or greater of follow-up, sufficient support was provided to use a broadened window of 7 to 14 days for follow-up. This revised follow-up time frame will be included in labeling.

- *Allowing providers other than physicians to provide Mifeprex*: The current Prescriber's Agreement in the REMS specifies that "…Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications…" In addition, current labeling states that Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. However, labeling states that other healthcare providers, acting under the supervision of a qualified physician, may also provide Mifeprex to patients. Several published studies submitted by the Applicant indicate that health care providers such as nurse practitioners, nurse midwives, and physician assistants are

[37] Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. Contraception 2006;74:36-41.
[38] Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? Contraception 2015;91:6-11.
[39] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

currently providing abortion services. One of these studies (Kopp Kallner et al[40]) was a randomized controlled trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. Success rates were ≥ 96% regardless of gestational age. The nurse midwife group had few complications, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, p=0.14). No serious complications were reported and no blood transfusions were administered in the study. Based on this and other supportive studies, the information supports the efficacy and safety of allowing healthcare providers other than physicians can effectively and safely provide abortion services, provided that they meet the requirements for certification described in the REMS. The clinical team also felt that the term "healthcare provider who prescribes" would be the appropriate terminology as prescribing ability is a critical factor in dispensing Mifeprex.

The clinical review team concluded that the evidence demonstrated acceptable safety for each of the above proposed changes, and I concur with their conclusion. The proposed dosing regimen has a similar safety profile as the original regimen approved in 2000. Adverse outcomes of interest, such as deaths, serious infection, transfusions, ectopic pregnancies and uterine rupture, remain rare, and are not necessarily attributable to Mifeprex use. Overall, the rate of deaths and nonfatal serious adverse events are acceptably low, and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen No association between adverse outcomes and increasing gestational age was identified. Finally, the available information supports the safety of the other proposed changes, including increasing the flexibility of the time interval between Mifeprex and misoprostol, at home use of misoprostol, use of a repeat dose of misoprostol, change in the follow-up timeframe and allowing health care providers other than physicians to prescribe and dispense Mifeprex were acceptable.

9. Advisory Committee Meeting

Mifeprex is not a new molecular entity requiring discussion before an advisory committee. In addition, an advisory committee was not necessary as the application did not raise complex scientific or other issues that would warrant holding an AC before approval.

10. Pediatrics

This efficacy supplement triggered requirements under the Pediatric Research Equity Act (PREA). The Agency granted a partial PREA waiver for pre-menarcheal females ages birth to 12 years because it would be impossible to conduct studies in this pediatric population, as pregnancy does not exist in premenarcheal females.

[40] Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. Human Reprod 2010;25(5):1153-1157.

The Applicant fulfilled the remaining PREA requirement in postmenarcheal females by submitting published studies of Mifeprex for pregnancy termination in postmenarcheal females less than 17 years old. Efficacy and safety information in these adolescents was based on a U.S. study in 322 postmenarcheal adolescents (Gatter et al[41]). Of the 322 adolescents, 106 of these adolescents were under 16; see Table 2 below:

Table 2: Age and Number of Adolescents Undergoing Medical Abortion (Gatter et al[42])

Age of Subject	Number of Subjects evaluated
11	1
12	1
13	2
14	20
15	82
16	216

Source: Refer to Table 17 of the Medical Officer's review dated March 29, 2016

The Gatter et al[43] study reported that postmenarchal females less than 18 years old had a 98.7% pregnancy termination rate as compared to females aged 18-24, who had a rate of 98.1%. This article reported that loss to follow-up was slightly higher in those less than 18 years old, however, age did not adversely impact efficacy outcomes.

One issue was whether adolescents would comply with at home use of misoprostol. The Gatter[44] et al study incorporated at home use of misoprostol into the Mifeprex dose regimen given to all females, including postmenarchal females less than 18 years old. The overall efficacy in adolescents was similar to that of all older women. This information supports at home administration of misoprostol in postmenarchal females under 17.

Two other published studies provided additional efficacy on Mifeprex use by adolescents for pregnancy termination:

- Phelps et al[45] evaluated data from 28 adolescents aged 14 to 17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. In this study, 100% of subjects had a complete pregnancy termination, with five not requiring misoprostol.

[41]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[42] Ibid.
[43]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[44]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[45]Phelps RH, et al. Mifepristone abortion in minors. Contraception 2001;64:339-343.

- Niinimaki et al[46] used data from a Finnish Registry from 2000-2006. An analysis of efficacy between adolescents under age 18 compared to the women ≥ age 18 indicated that the adolescent group had a lower rate of incomplete abortions as compared to adults. And efficacy outcomes in adolescents were similar to those of adult women.

The safety of Mifeprex in postmenarcheal adolescents was primarily supported by adverse event information from the Gatter et al[47] study. (b) (6), (b) (4) Supportive data from a Finnish registry (Niinimaki et al) from 3024 adolescent females under 18 years of age reported that, compared to adult women, the risks of hemorrhage (adjusted odds ratio 0.87 [95% confidence interval: 0.77 to 0.99]), incomplete abortion (0.69, [95% confidence interval: 0.59 to 0.82]), and surgical evacuation (0.78, [95% confidence interval: 0.67 to 0.90]) were lower in the adolescent cohort. In the Finnish registry study, a majority of adolescents and adults received both Mifeprex and misoprostol. Safety findings from the Gatter et al and Niinimaki et al studies are reassuring and indicate that the safety profile of Mifeprex is similar between postmenarcheal adolescents and adult women.

Additional details from this article and other published data on Mifeprex use in adolescents (females under 17) are described in the clinical review (Refer to the Medical Officer's review dated March 29, 2016).

(b) (6) concurred that the efficacy and safety data in postmenarcheal adolescents less than 17 years old was sufficient to support the use of Mifeprex in this pediatric population and to fulfill the PREA pediatric study requirement. The revised Mifeprex labeling will state that that efficacy and safety are similar to adult women in the Pediatric Use section (8.4).

11. Other Relevant Regulatory Issues

(b) (6)

reviewed the Medication Guide in conjunction with the (b) (6) ((b) (6) Both (b) (6) and (b) (6) found the Medication Guide to be acceptable with recommended changes (See review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in

[46]Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.
[47]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[48]Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

the Medication Guide and incorporated appropriate changes into the final agreed upon Medication Guide.

(b) (6) (b) (6)

(b) (6) reviewed the Prescribing Information (PI) in addition to the joint review with (b) (6) of the Medication Guide in conjunction with (b) (6) After review, (b) (6) provided recommended changes (See (b) (6) review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in the PI and incorporated appropriate changes into the final label.

(b) (6) (b) (6)

(b) (6) (b) (6) in the (b) (6)) reviewed the proposed modifications to the REMS. The (b) (6) review reflected agreement with the Applicant's proposed REMS changes which include:

- Removal of the term "under Federal law" from the Prescriber's Agreement.
- Replacement of the word "physician" with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex. (b) (6) believes that the Applicant's proposed terminology of " (b) (4) is too broad and that a more appropriate description is "healthcare provider who prescribes," which limits acceptable healthcare providers to those who are licensed in their state to prescribe medications.
- Removal of the Medication Guide from the REMS. The Medication Guide remains an important education tool for patients. It will still be dispensed to each patient in accordance with 21 CFR part 208. As described in the Medication Guide Guidance, a Medication Guide is not necessary to ensure that the benefits outweigh the risks of Mifeprex
- Modification of Element to Assure Safe Use (ETASU) A, the Prescriber's Agreement. (b) (6) recommends changing the name of the document to the Prescriber's Agreement Form to be consistent with other REMS programs. References to "physician" should be changed to "healthcare provider who prescribes."
- (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
  1. The established safety profile over 15 years of experience with Mifeprex is well-characterized, stable, and known serious risks occur rarely
  2. The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208
  3. The Prescriber's Agreement Form will continue to require providers to explain the treatment, its effects and risks associated with Mifeprex and to answer any questions that a patient may have
  4. Established clinical practice provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment. FDA has removed REMS

requirements in other programs based on the integration of the REMS safe use condition into clinical practice.

Other revisions to the REMS document will be made for consistency with changes described above and to reflect current FDA thinking and practice regarding format, language and flow in REMS documents. These changes include modification of the Mifeprex REMS goal, changes in requirements to certify prescribers (removal of the requirement to obtain a Patient Agreement) and other minor edits.

In summary, the overall (b) (6) recommendation for the REMS modification for this efficacy supplement was approval (Refer to (b) (6) review dated March 29, 2016).

12. Labeling

Carton and container labeling was reviewed by the (b) (6) (b) (6) the (b) (6) (b) (6) and the (b) (6) (b) (6) (b) (6) Their comments were conveyed to the Applicant as appropriate.

The label was submitted in the format prescribed by the PLR. Although the supplement was submitted prior to when it would otherwise have been required to comply with the PLLR requirements, the review team believed it would be of value to harmonize with this labeling standard to the extent possible.

Specific issues discussed during labeling negotiations included the selection of studies for inclusion in Section 6.1 (Clinical Trial Experience in the ADVERSE REACTIONS section) and 14 (CLINICAL STUDIES section). Only studies that evaluated the specific proposed regimen were included in these sections. For the Adverse Reactions section, examination of the common adverse reaction data by U.S. compared to non-U.S. study location revealed that there were large differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the U.S. studies. This may reflect differences in ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data would not be appropriate, as it is unlikely to be informative to the U.S. population of users. In the case of serious adverse reactions, the reported frequency was quite similar regardless of study location; for this reason, serious adverse reaction information from global studies is reported.
Agreement on labeling was reached on March 29, 2016.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

Postmarketing Requirements/Postmarketing Commitments: None.

Risk Evaluation and Mitigation Strategies (REMS): The Applicant proposed a REMS modification for the Mifeprex REMS program with the submission of this efficacy supplement. The review teams from the (b) (6) evaluated the current Mifeprex REMS program and the proposed REMS modifications to determine whether each Mifeprex REMS element remains necessary to ensure that the benefits of Mifeprex outweigh the risks. Factors that impacted the decision included findings from two REMS assessments (the more recent REMS assessment review was completed in October 2015), an unchanged safety profile, and published literature that documented adequate safeguards in clinical practice with the use of Mifeprex in a regimen with misoprostol.

The teams determined that the following REMS modifications were warranted:

1. Revisions to the Prescriber Agreement Form to reflect the new dosing regimen and to reflect current REMS formatting and language standards
2. Removal of the Medication Guide as a REMS element, as distribution of the Medication Guide is required under 21 CFR 208
3. Removal of the Patient Agreement as a Documentation of Safe Use Condition (ETASU D)
4. Updating of the REMS goals to reflect the above 3 changes.
5. Removal of the phrase "Under Federal law" from the Prescriber's Agreement
6. Replacing the term "licensed physician" with "healthcare provider who prescribes"

The above modifications to the Mifeprex REMS program were discussed with the (b) (6) (b) (6) on January 15, 2016, as per (b) (6) .

The (b) (6) concurred with conforming changes to the Prescriber's Agreement to reflect the new dosing regimen, and with removal of the Medication Guide from the REMS. The Medication Guide would remain a part of labeling to inform patients about the risks associated with Mifeprex use. The (b) (6) also concurred with revisions to the REMS goals to reflect these changes.

The (b) (6) concurred with the removal of the term "under Federal law". A rationale for the original inclusion of the phrase "Under Federal law" cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and it was decided that the phrase be removed from the Prescriber's Agreement.

The (b) (6) concurred with use of the term "healthcare providers who prescribe." To support a change in the REMS that would allow qualified healthcare providers other than physicians to prescribe Mifeprex through the Mifeprex REMS program, the Applicant provided information from over 3,200 women in randomized controlled trials and 596 women in prospective cohort studies comparing medical abortion care by physicians versus other providers (nurses or nurse midwives). These studies were conducted in a variety of settings (international, urban, rural, and low-resource). No differences in serious adverse events, ongoing pregnancy or incomplete abortion were identified between the groups. Given that providers other than physicians are providing family planning and abortion care under supervision and that the approved labeling and REMS program stipulate that prescribers must be able to refer patients for additional care, including surgical management, allowing these prescribers to participate in the Mifeprex REMS program is acceptable.

The (b) (6) also concurred with the teams' recommendation to remove the Patient Agreement (ETASU D) from the REMS although some (b) (6) members commented that additional support for the review team's rationale for this modification was needed. The review team's rationale for this change was:

APPEARS THIS WAY ON ORIGINAL

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and Informed Consent, and, more specifically with Mifeprex, includes counseling on all options for termination of pregnancy, access to pain management and emergency services if needed.
- Medical abortion with Mifeprex is provided by a well-established group of organizations and their associated providers who are knowledgeable in this area of women's health. Their documents and guidelines cover all the safety information that also appears in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the direct supervision of a certified prescriber.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

The Mifeprex REMS program will have a modified ETASU REMS that will continue to ensure that Mifeprex can only be prescribed by certified prescribers and be dispensed to patients in certain healthcare settings, specifically, clinics, medical offices and hospitals. The Medication Guide will continue to be distributed to patients required under 21 CFR part 208. As required for all ETASU REMS, ongoing assessments of the Mifeprex REMS program will continue to ensure that the modified Mifeprex REMS program is meeting its goals.

13. Decision/Action/Risk Benefit Assessment

Decision:

All regulatory and scientific requirements have been adequately addressed in this efficacy supplement. Review teams involved in this supplement have recommended approval of the supplement from their disciplines' perspective. The submitted efficacy and safety information supported approval of the proposed dosing regimen through 70 days gestation, and other changes discussed in this summary memo. This supplement will receive an Approval action.

Benefit Risk Assessment:

This efficacy supplement provided substantial evidence of efficacy for the proposed dosing regimen through 70 days gestation. The efficacy findings were similar to those that led to the approval of the original dosing regimen in 2000. In addition, the submitted published literature supported other changes sought in this efficacy supplement that will

be reflected in labeling: 1) a more flexible time interval of 24 to 48 hours between Mifeprex and misoprostol administration, 2) the option of at home administration of misoprostol, 3) the option of repeat misoprostol dosing, if clinically indicated, 4) flexibility in the follow–up time frame of 7 to 14 days, and 5) permitting qualified healthcare providers other than physicians to prescribe Mifeprex.

The safety findings of the proposed dosing regimen were acceptable and were similar to those seen with the original dosing regimen approved in 2000.

After review of the REMS modifications proposed by the Sponsor, I concur with the clinical team and (b) (6) recommendations that:

1. The Medication Guide can be removed from the Mifeprex REMS program. The Medication Guide requirements under 21 CFR part 208 require the Medication Guide to be distributed to patients. Mifeprex will only be dispensed by a healthcare professional who will be knowledgeable and able to provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or follow-up that may be required as appropriate, and who will answer any questions the patient may have. In that setting, the Medication Guide will already be a required available tool for counseling. Therefore, given the existing requirements under 21 CFR part 208, I concur that there is no reason for the Medication Guide to specifically be a part of the REMS.

2. The Prescriber Agreement Form (ETASU A) as revised reflects current FDA format and content to conform to current REMS programs and reflect the labeling changes that will be approved in this supplement. I concur that the changes are acceptable.

3. Revision of the Mifeprex REMS goals (ETASU C) will adequately mitigate the risk of serious complications by requiring certification of healthcare providers who prescribe and ensuring the Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber.

4. Removal of the Patient Agreement Form (ETASU D): I concur with the clinical review team that the Patient Agreement Form, which requires a patient's signature, does not add to safe use conditions for the patient for this REMS and is a burden for patients. It is standard of care for patients undergoing pregnancy termination to undergo extensive counseling and informed consent. The Patient Agreement Form contains duplicative information already provided by each healthcare provider or clinic. I believe that it is much more critical for the healthcare provider who orders or prescribes Mifeprex to provide and discuss informed consent derived from their own practice so that care can be individualized for the patient.

I support that the Mifeprex REMS with ETASUs A and C remain in place to support conditions critical to the use of the drug. Therefore, the implementation system and timetable for assessments should continue.

I also agree with the clinical review team that the reporting requirements should only be required for deaths. It is important that the Agency be informed of any deaths with Mifeprex to monitor new safety signals or trends. However, after 15 years of reporting serious adverse events, the safety profile for Mifeprex is essentially unchanged. Therefore, I agree that reporting of labeled serious adverse events other than deaths can be collected in the periodic safety update reports and annual reports to the Agency.

In summary, I believe that the benefit-risk profile for Mifeprex continues to be favorable and with the agreed-to labeling changes and REMS modifications, the Mifeprex REMS program will continue to assure safe use. Therefore, I support approval of this efficacy supplement and REMS modifications.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked [redacted] (b) (6) and the [redacted] (b) (6) to continue to include a Patient Agreement Form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through the [redacted] (b) (6) (6) Therefore, the Patient Agreement Form will be retained and other changes will be made in the REMS to reflect that it is being retained.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

No. 23-10362

IN THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

ALLIANCE FOR HIPPOCRATIC MEDICINE; AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS; AMERICAN COLLEGE OF PEDIATRICIANS; CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS; SHAUN JESTER, D.O.; REGINA FROST-CLARK, M.D.; TYLER JOHNSON, D.O.; GEORGE DELGADO, M.D.,

Plaintiffs-Appellees,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, Commissioner of Food and Drugs; JANET WOODCOOK, M.D., in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration; PATRIZIA CAVAZZONI, M.D., in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, Secretary, U.S. Department of Health and Human Services,

Defendants-Appellants,

DANCO LABORATORIES, L.L.C.,

Intervenor-Appellant.

ADDENDUM TO EMERGENCY MOTION FOR A STAY PENDING APPEAL

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MAR 29 2016

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Re: Docket No. FDA-2002-P-0364

Dear Drs. Harrison and Rudd and Ms. Nance:

This letter responds to your citizen petition submitted on August 20, 2002, to the Food and Drug Administration (FDA or Agency) on behalf of the American Association of Pro Life Obstetricians and Gynecologists (AAPLOG), the Christian Medical Association (CMA) (n/k/a the Christian Medical and Dental Associations), and Concerned Women for America (CWA) (Petition).[1] Your Petition requests that the Agency stay FDA's approval of Mifeprex (mifepristone, also known as RU-486), thereby halting the distribution and marketing of the drug pending final action on the Petition. The Petition also requests that the Agency revoke FDA's approval of Mifeprex and requests a full audit of the French and U.S. clinical trials submitted in support of the new drug application (NDA) for Mifeprex.

We have carefully considered the information submitted in your Petition, comments on your Petition submitted to the docket, other submissions to the docket, and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your Petition is denied.

[1] The citizen petition was originally assigned docket number 2002P-0377/CP1. The number was changed to FDA-2002-P-0364 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. This citizen petition was submitted by AAPLOG, CMA, and Sandy Rios, the then-President of CWA. We have addressed this response to CWA's current CEO and President, Penny Young Nance.

I. BACKGROUND

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets eight qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments[2] that the then-applicant of the Mifeprex NDA (i.e., the Population Council)[3] agreed to meet. In addition, the letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

II. DISCUSSION OF ISSUES RAISED

You maintain that good cause exists for granting an immediate stay of the Mifeprex approval and for the subsequent revocation of that approval under 21 CFR 314.530 (Petition at 3). You contend that:

- The approval of Mifeprex in 2000 violated the Administrative Procedure Act's (APA's) prohibition against agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (5 U.S.C. 706(2)(A));
- The 2000 approval violated section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355) because Mifeprex does not satisfy the safety and labeling requirements of that section; and
- FDA approved Mifeprex in 2000 despite the presence of substantial risks to women's health, including fatal hemorrhage and serious bacterial infections.

You make eight arguments for the stay and revocation of the 2000 Mifeprex approval, as follows (Petition at 4-7):

[2] For purposes of this petition response, the term 'Phase 4 commitments' refers to the postmarketing studies that the Mifeprex sponsor agreed to perform as a condition of approval.

[3] Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco), which had been licensed to manufacture and market Mifeprex.

- That the approval of Mifeprex in 2000 violated the legal requirements of the accelerated approval regulations under 21 CFR Subpart H.
- That Mifeprex was not proven safe and effective in 2000 as required by law.
- That the Mifeprex regimen requires that Mifeprex be used in conjunction with another drug, misoprostol, which has not been separately approved as an abortifacient.
- That the Mifeprex regimen was approved in 2000 without adequate safety restrictions.
- That the drug's sponsor, following the approval in 2000, neglected to require Mifeprex providers to adhere to the restrictions contained in the regimen approved at that time.
- That the safeguards employed in one of the clinical trials that supported the 2000 approval were not mirrored in the regimen that FDA approved.
- That FDA improperly waived a requirement for pediatric studies in connection with the 2000 Mifeprex approval.
- That FDA did not require the sponsor of Mifeprex to honor its commitments for Phase 4 studies.

We respond to each of these arguments below.

We note your petition challenges the original approval of Mifeprex in 2000, and therefore this response is addressed to the 2000 approval and to the labeling that was approved at that time. Today, the Agency is approving a supplemental NDA submitted by Danco Laboratories, LLC (Danco), the holder of the Mifeprex NDA. This supplemental NDA proposed modified labeling for Mifeprex, including an updated dosing regimen, and included data to support the new labeling. After reviewing Danco's supplemental NDA, FDA determined that it met the statutory standard for approval. The fact that the previously approved regimen is no longer included in the labeling does not reflect a decision that there were safety or effectiveness concerns with the previously approved regimen.

A. Approval of Mifeprex Was Consistent With Subpart H

You maintain that FDA's 2000 approval of Mifeprex under the subpart H regulations was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, and thus violated the APA (Petition at 18-23). You state that pregnancy, without major complications, is not a serious or life-threatening illness; instead, you claim it is a normal physiological state experienced by most females one or more times and is rarely accompanied by life-threatening complications (Petition at 19). You contend that Mifeprex does not provide meaningful therapeutic benefit to patients over existing treatments because surgical abortion is a less dangerous, more effective alternative for the termination of pregnancy, and that Mifeprex does not treat any subset of the female population that is unresponsive to or intolerant of surgical abortion

(Petition at 21-23). Thus, you assert that the approval of Mifeprex did not meet the requirements for product approval under subpart H (Petition at 23).

We disagree with your conclusion that we inappropriately approved Mifeprex under subpart H. As stated in section I above, the accelerated approval regulations apply to new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (§ 314.500). As FDA made clear in the preamble to the final rule for subpart H, the subpart H regulations are intended to apply to serious or life-threatening conditions, as well as to illnesses or diseases.[4] The Agency also made clear that a condition need not be serious or life-threatening in all populations or in all phases to fall within the scope of these regulations.[5] Unwanted pregnancy falls within the scope of subpart H under § 314.500 because unwanted pregnancy, like a number of illnesses or conditions, can be serious for certain populations or under certain circumstances.

Pregnancy can be a serious medical condition in some women.[6] Pregnancy is the only condition associated with preeclampsia and eclampsia and causes an increased risk of thromboembolic complications, including deep vein thrombophlebitis and pulmonary embolus. Additionally, there is a significant risk of a major surgical procedure and anesthesia if a pregnancy is continued; for 2013 (the most recent data available), the Centers for Disease Control and Prevention reported an overall 32.7 percent rate of cesarean sections in the United States.[7] Other medical concerns associated with pregnancy include the following: disseminated intravascular coagulopathy (a rare but serious complication); amniotic fluid embolism; life-threatening hemorrhage associated with placenta previa, placenta accreta, placental abruption, labor and delivery, or surgical delivery; postpartum depression; and exacerbation or more difficult management of preexisting medical conditions (e.g., diabetes, lupus, cardiac disease, hypertension). In addition, approximately 50 percent of all pregnancies in the United States each year are unintended.[8] According to the

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[4] See, e.g., 57 FR 58942, 58946 (Dec. 11, 1992).

[5] Id.

[6] According to data from the Centers for Disease Control and Prevention (CDC), for 2012 (the most recent year for which data are available), the pregnancy-related mortality ratio in the United States was 15.9 maternal pregnancy-related deaths per 100,000 live births. See CDC, Pregnancy Mortality Surveillance System, available on the CDC Web page at http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html. A 2012 study by Raymond and Grimes provides a comparison for the mortality rate associated with legal abortion to live birth in the United States for the earlier period from 1998 through 2005. Investigators reported that over the study period, the pregnancy related mortality rate among women who delivered live neonates was 8.8 deaths per 100,000 live births. This lower rate excludes deaths from ectopic pregnancies, stillbirths, gestational trophoblastic disease, etc. During the same period, the rate of abortion related mortality was 0.6 per 100,000 abortions. The risk of childbirth related death was therefore approximately 14 times higher than the rate associated with legal abortion. Raymond, EG and DA Grimes, Feb. 2012, The Comparative Safety of Legal Induced Abortion and Childbirth in the United States, Obstet Gynecol, 119 (2, Part 1):215-219.

[7] See CDC, Nov. 5, 2014, Trends in Low-risk Cesarean Delivery in the United States, 1990-2013, National Vital Statistics Report, 63(6), available at http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_06.pdf .

[8] Guttmacher Institute, Feb. 2015, Unintended Pregnancy in the United States, at 1, available at http://www.guttmacher.org/pubs/FB-Unintended-Pregnancy-US.pdf. See also Institute of Medicine, 2011,

Institute of Medicine, women experiencing an unintended pregnancy may experience depression, anxiety, or other conditions.[9]

Furthermore, consistent with § 314.500, medical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion.[10] Although FDA provided several examples in the preamble to the final rule to illustrate how the term "meaningful therapeutic benefit" might be interpreted, the Agency did not suggest that the meaning of the term was limited to the examples provided.[11] In the Phase 3 clinical trial of Mifeprex conducted in the United States, medical termination of pregnancy avoided an invasive surgical procedure and anesthesia in 92 percent of the 827 women with an estimated gestational age (EGA) of 49 days or less.[12] Complications of general or local anesthesia, or of intravenous sedation ("twilight" anesthesia), can include a severe allergic reaction, a sudden drop in blood pressure with cardiorespiratory arrest, death, and a longer recovery time following the procedure. Medical (non-surgical) termination of pregnancy provides an alternative to surgical abortion; it is up to the patient and her provider to decide whether a medical or surgical abortion is preferable and safer in her particular situation.[13]

Clinical Preventive Services for Women: Closing the Gaps (Closing the Gaps), at 102-110, available at http://books.nap.edu/openbook.php?record_id=13181 (stating that "[u]nintended pregnancy is highly prevalent in the United States").

[9] See Closing the Gaps, supra note 8, at 103.

[10] For a discussion of how FDA interprets the phrase "meaningful therapeutic benefit to patients over existing treatments" in 21 CFR 314.500, see FDA guidance for industry, *Expedited Programs for Serious Conditions—Drugs and Biologics*, at 3-4, 16-17, available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[11] 57 FR 58942, 58947 (Dec. 11, 1992).

[12] FDA, 1999, Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion Up to 63 Day Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments (Medical Officer's Review), at 11 (Table 1) and 16, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf and http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P2.pdf. Spitz, IM, et al., 1998, Early Pregnancy Termination With Mifepristone and Misoprostol in the US, NEJM, 338:1241-1243.

[13] CDC data indicate that for the 730,322 abortions reported in 2011, there were 2 deaths. The CDC's calculated case fatality rate over the period from 2008 to 2011 (the most recent year for which data are available), the case fatality rate was 0.73 legal induced abortion-related deaths per 100,000 reported legal abortions. http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6410a1.htm?s_cid=ss6410a1_e. Mortality rates identified by type of abortion (medical or surgical) were not available. However, the evidence suggests that the risk of mortality associated with medical abortion is quite low. Confirmation of the low risk of medical abortion is provided in a study by Trussell, et al., which recorded no deaths for 711,556 medical abortions performed by Planned Parenthood clinics under the buccal misoprostol administration protocol (Trussell J, D Nucatola, et al., Mar. 2014, Reduction in Infection-Related Mortality Since Modifications in the Regimen of Medical Abortion, Contraception, 89(3):193-6). We note that one study reported a comparatively high occurance of fatality (1 death in a study of 11,155 early medical abortions); however, this apparent high occurence of fatality is likely due to instability in the estimate as a result of the small sample size (Goldstone P, J Michelson, et al., Sept. 3, 2012, Early Medical Abortion Using Low-Dose Mifepristone Followed by

You cite a study by Jensen, et al., as support for your claim that surgical abortion is less dangerous and more effective than Mifeprex (Petition at 21-22 (citing Jensen, JT, et al., 1999, Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study, Contraception, 59:153-159 (Jensen study)). This study was a prospective, nonconcurrent cohort analysis comparing the patients from one site in the U.S. phase 3 trial and a separate group of patients (who were not part of the U.S. phase 3 trial) who underwent surgical abortion at the same facility. The populations that were compared were not randomized to treatment (i.e., medical or surgical abortion) and the treatment periods did not overlap.[14] In addition, the data on medical abortion cited in the Jensen study are based on the 178 subjects at a single site in the phase 3 U.S. Mifeprex trial that enrolled 2,121 women. This small subset of the U.S. trial included patients with pregnancies of up to 63 days' gestation. Although you cite a surgical intervention rate of 18.3 percent in the Mifeprex patients, the surgical intervention rate for Mifeprex patients with an EGA ≤ 49 days was 12.7 percent (9 of 71), which, because of the small number of patients in the two groups, is not statistically significantly different from the 3.9 percent rate for re-intervention in the comparative surgical group (3 of 77).[15] Furthermore, the 3.9 percent who first had a surgical abortion and then required surgical re-intervention ultimately required *two* surgical interventions, not one, thereby exposing them twice to the risks inherent in invasive surgical procedures and anesthesia. Finally, although you state that the medical abortion patients in the Jensen study reported significantly longer bleeding than did surgical patients, there was not a greater amount of bleeding in the medical abortion group, nor was there a significant difference between the two treatment groups in the incidence of anemia as determined by the overall change in hemoglobin concentrations.

You state that FDA "viewed [s]ubpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe" (Petition at 23 (footnote omitted)). The question of whether subpart H was "the only available regulatory vehicle" is not relevant here. As described above, Mifeprex met the criteria for approval under subpart H. Additionally, as stated in the September 28, 2000, memorandum to NDA 20-687 (Mifeprex Approval Memorandum), "the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications" that were set out in the approval letter and the Prescriber's Agreement.[16]

Buccal Misoprostol: A Large Australian Observational Study, Med J Aust, 197(5):282-6). Much more accurate and meaningful data are provided by Trussell's study covering >700,000 medical abortions.

[14] We are not suggesting that in order to be adequate and well-controlled a trial must be concurrently controlled. As discussed below in section II.B.1, FDA's regulations in § 314.126 recognize a number of different types of controls.

[15] In addition, the mean surgical intervention rate for all Mifeprex patients with gestational ages ≤ 49 days in the Phase 3 U.S. trial was 7.9 percent (65 of 827 evaluable patients).

[16] FDA, Sept. 28, 2000, Memorandum to NDA 20-687 MIFEPREX (mifepristone) Population Council (Mifeprex Approval Memorandum), available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111366.pdf

Furthermore, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[17] The2011 REMS for Mifeprex incorporated the restrictions under which the drug was approved. Indeed, there is substantial overlap between the requirements of subpart H and the statutory criteria for REMS set out in Title IX.

Given all of the above, the Mifeprex NDA was appropriately approved in 2000.

B. The French and U.S. Clinical Trials of Mifeprex Provided Substantial Evidence to Support Approval

You contend that the studies on which the Population Council relied in support of its NDA for Mifeprex do not meet the statutory and regulatory requirements for the quality and quantity of scientific evidence needed to support a finding that a new drug is safe and effective (Petition at 24).

Our review of Mifeprex was thorough and consistent with the FD&C Act and FDA regulations, including the requirements under section 505(d) of the FD&C Act that: (1) there be adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling (section 505(d)(1)) and (2) there be substantial evidence that the drug will have the effect it purports or is recommended to have under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d)(5)). The Mifeprex NDA was thoroughly reviewed, and the drug product was found to be safe and effective for its approved indication. In addition, as noted in the Mifeprex Approval Memorandum (at 1), FDA's Reproductive Health Drugs Advisory Committee (Advisory Committee) voted 6 to 0 (with 2 abstentions) on July 19, 1996, that the benefits of Mifeprex exceeded the risks. As set forth below, we disagree with your claims concerning the clinical trials that form the basis for the approval of Mifeprex.

1. The Clinical Trials Used to Support the Mifeprex NDA Were in Accordance With the FD&C Act and Applicable Regulations

You argue that because neither the French clinical trials nor the U.S. clinical trial of mifepristone were blinded, randomized, or concurrently controlled, these trials were inadequate to establish the safety and effectiveness of Mifeprex (Petition at 24-25 and 32-34). In addition, you assert in the response you submitted on October 10, 2003, to the comments in opposition to the Petition submitted by the Population Council and Danco (Response to Opposition) that the clinical trials of Mifeprex were not historically controlled but instead were uncontrolled.[18] You state that the

[17] 73 FR 16313 (Mar. 27, 2008).

[18] Response to Opposition at 5. You also state that because the Mifeprex regimen was the first drug regimen that FDA approved to induce abortions, the applicant should have compared the new drug regimen to surgical abortions performed during the first 49 days after a woman's last menstrual period (Response to Opposition at

applicant did not describe any historical control group in the French clinical trials, and did not indicate that any of the scientific guidelines for selecting a proper control group before beginning a historically controlled study were used for these trials (id. at 5-6). You also reject the applicant's claim that the available information on surgical abortion constitutes historically controlled data (id. at 6).

We disagree with your conclusion that the French and U.S. clinical trials of mifepristone were not clinically and legally adequate to support the approval of Mifeprex. The data from these three clinical trials (a large U.S. trial and two French trials) constitute substantial evidence that Mifeprex is safe and effective for its approved indication in accordance with section 505(d) of the FD&C Act. The labeling approved in 2000 for Mifeprex was based on data from these three clinical trials and from safety data from a postmarketing database of over 620,000 women in Europe who had had a medical termination of pregnancy (approximately 415,000 of whom had received mifepristone together with misoprostol).[19]

The U.S. trial of Mifeprex involved 2,121 subjects enrolled at 17 sites. Of these, 827 had an EGA of ≤ 49 days and were included in the efficacy evaluation.[20] Medical termination of pregnancy was complete (without the need for surgical intervention) in 762 of these subjects (92 percent).[21] Sixty-five of the subjects in the U.S. trial who were evaluable for efficacy were classified as having had a "treatment failure." The reasons for treatment failure (and number of subjects experiencing each) were: incomplete pregnancy termination (n = 39), still pregnant (n = 8), subject request for surgical intervention (n = 5), and medical indication (bleeding, n = 13).[22] The two French trials enrolled a total of 1,681 subjects providing effectiveness outcomes. Among the French subjects, the success rate for medical termination of pregnancy was 95.5 percent.[23]

In the U.S. trial, 859 subjects with an EGA of ≤ 49 days were evaluated for safety. Among these subjects, there were no deaths, one transfusion, and nine instances in which subjects received intravenous fluids.[24] The safety profile of the patient group in the French trials with an EGA of ≤ 49 days did not differ significantly from the safety profile of the same patient group in the U.S.

5, note 20). The fact that a drug might be the first one approved for a particular indication is not a factor in determining what type of control is adequate for a clinical trial of that drug for that indication. As discussed above, FDA's regulations provide for a variety of different types of controls (see 21 CFR 314.126(b)), and do not require comparison of a proposed drug product to an active control group to establish the safety and effectiveness of the drug. Therefore, the clinical trials to support the approval of Mifeprex were not required to have a surgical comparator arm.

[19] Mifeprex labeling, Sept. 28, 2000, PRECAUTIONS, Teratogenic Effects: Human Data, *Pregnancy*, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf.

[20] Mifeprex Approval Memorandum, supra note 16, at 1; Medical Officer's Review, supra note 12, at 10.

[21] Medical Officer's Review, supra note 12, at 11 (Table 1) and 16.

[22] Id. at 11 (Table 1).

[23] Mifeprex Approval Memorandum, supra note 16, at 1.

[24] Medical Officer's Review, supra note 12, at 12-13.

trial, and the percentage of patients in the French and U.S. trials requiring hospitalization and blood transfusion and experiencing heavy bleeding was comparable.[25] There were no deaths in the French trials.[26]

Section 505(d) of the FD&C Act states, in part, that FDA must refuse to approve an application if the Agency finds that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the drug's proposed labeling. Section 505(d) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

As stated in 21 CFR 314.126(a), the purpose of conducting clinical investigations of a drug is to distinguish the effect of the drug from other influences, such as a spontaneous change in the course of the disease or condition, placebo effects, or biased observation. Reports of adequate and well-controlled investigations serve as the main basis for determining whether there is substantial evidence to support the claims of effectiveness for a drug.

We agree that randomization and the use of concurrent controls are two principal means of ensuring that clinical trial data are reliable and robust. However, that does not mean that in order to be adequate and well-controlled, a clinical trial must use a randomized concurrent control design. Section 314.126(b) lists the characteristics of an adequate and well-controlled study. Contrary to your assertion (Petition at 24), FDA regulations do not require that a study be blinded, randomized, and/or concurrently controlled. Among the characteristics of an adequate and well-controlled study is that it uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect (§ 314.126(b)(2)). A historical control is one of the recognized types of control (§ 314.126(b)(2)(v)), and one in which the results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment in comparable patients or populations (id.). Unlike some other types of control (e.g., placebo concurrent control (§ 314.126(b)(2)(i)) or dose-comparison concurrent control (§ 314.126(b)(2)(ii))), use of a historical control does not include randomization or blinding. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances, including studies in which the effect of the drug is self-evident.[27] Thus, in the proper setting,

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[25] Id. at 18.

[26] FDA, May 21, 1996, Statistical Review and Evaluation (May 21, 1996, Statistical Review), at 4 and 7, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

[27] 21 CFR 314.126(b)(2)(v). We note your contention that the effects of the regimen approved in 2000 are not self-evident because "[t]he Sponsor's focus on this dyadic set of possibilities (failure (0) or success (1)) obscures a whole range of less easily measurable, but critically important, outcomes," including "tissue retention, life-threatening hemorrhaging, persistent bleeding, infection, teratogenicity, pain, continued fertility, and psychological effects" (Response to Opposition at 8). We disagree with your argument. From a clinical perspective, there are two outcomes associated with the use of Mifeprex for medical abortion: either there is a complete abortion (without the need for surgical intervention) or there is not. The "outcomes" you

historically controlled trials can be considered adequate and well-controlled, and there is no need for the other types of control listed in § 314.126(b)(2).[28]

The use of historical controls in the Mifeprex clinical trials was appropriate for two reasons. First, the natural history of a viable pregnancy is adequately documented (a pregnancy continues on average for 40 weeks' gestation).[29] Second, the effect of Mifeprex is dramatic, occurs rapidly following treatment, and has a low probability of having occurred spontaneously.[30] Furthermore, contrary to your assertion (Petition at 32-34), the use of a historical control in these circumstances is consistent with ICH's guidance for industry, *E10 Choice of Control Group and Related Issues in Clinical Trials* (E10 Guidance).[31] The E10 Guidance addresses external controls (including historical controls) that are used in externally controlled trials to compare a group of subjects receiving the test treatment with a group of patients external to the study, rather than with an internal control group consisting of patients from the same population assigned to a different treatment.[32] The guidance states that the "external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome)."[33]

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cite are complications that can be associated with all abortions (including surgical abortion, missed abortion (non-viable pregnancy that has not been expelled from the uterus), and spontaneous abortion).

[28] You cite to a statement in the May 21, 1996, Statistical Review regarding the two French trials that "[i]n the absence of a concurrent control group in each of these studies, it is a matter of clinical judgement whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy" (Petition at 27). FDA's finding that Mifeprex was safe and effective for its labeled indication was based on data from three trials, one in the U.S. and two in France, as well as from safety data from a database of over 620,000 women in Europe who had had a medical termination of pregnancy (and approximately 415,000 of whom had received the combination of mifepristone and misoprostol). The Medical Officer's Review, supra note 12, also states that the "U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical abortions with gestations of 49 days duration or less" (Id. at 18-19). As stated previously, it is up to the physician and his/her patient to decide whether a medical or surgical abortion is preferable and safer in the patient's particular situation.

[29] MacDonald, PC, NF Gant, et al., 1996, Williams Obstetrics (20th ed.), Appleton and Lange, at 151.

[30] Although sources and studies differ somewhat, the 92% success rate following mifepristone/misoprostol use far exceeds the rate of spontaneous abortion (spontaneous miscarriage). One source states: "No less than 30% and as much as 60% of all conceptions abort within the first 12 weeks of gestation, and at least half of all losses go unnoticed. Most recognized pregnancy losses occur before 8 weeks' gestation, and relatively few occur after 12 weeks" (Fritz, M and L Speroff, 2011, Clinical Gynecologic Endocrinology and Infertility (8th ed.), Lippincott Williams & Wilkins, Philadelphia, at 1193). Other sources indicate that 15% of all pregnancies between 4-20 weeks of gestation spontaneously abort (See Speroff, L, et al., 1989, Clinical Gynecologic Endocrinology and Infertility (4th ed.), Williams and Wilkins, Baltimore, at 535; see also Stenchever, MA, 2001, Comprehensive Gynecology (4th ed.), Mosby, at 414). According to the National Library of Medicine, "[a]mong women who know they are pregnant, the miscarriage rate is about 15-20%. Most miscarriages occur during the first 7 weeks of pregnancy." (Miscarriage, available on the MedlinePlus Web site at http://www.nlm.nih.gov/medlineplus/ency/article/001488.htm.

[31] E10 Guidance, available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, at 6.

[32] Id.

[33] Id.

Moreover, the E10 Guidance clearly states that, notwithstanding certain limitations of external controls, including the possibility of bias, external controls can be appropriate under circumstances where the effect of the treatment is dramatic and the usual course of the disease or condition is highly predictable.[34] In other words, historical controls can be appropriate in circumstances such as medical termination of early pregnancy. The use of the expected rate of spontaneous abortion during early pregnancy as the control in the Mifeprex clinical trials was appropriate and fully consistent with FDA regulations and guidance. The applicant could rely on the data from the three trials to support approval because they were adequate and well-controlled, using a historical control.[35]

It is not uncommon for the drug product review divisions in FDA's Center for Drug Evaluation and Research (CDER) to accept for filing and approve applications that rely on clinical trials employing historical controls to support approval for drug products in which the outcome of the condition is well known and the effect of the drug is anticipated to be markedly different from that of a placebo. Examples include FDA's approval of numerous oncology drug products, including, for example, Xalkori (crizotinib) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test, and Adcetris (brentuximab vedotin) for the treatment of patients with Hodgkin lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. Other examples include iPlex (mecasermin rinfabate [rDNA origin] injection) for treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH; Myozyme (alglucosidase ALFA) for use in patients with Pompe disease (GAA deficiency); Ferriprox (deferiprone) for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate; Voraxaze (glucarpidase) for treatment of toxic (>1 micromole per liter) plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function; and Elelyso (taliglucerase alfa) for injection for use as a long-term enzyme replacement therapy in patients with Type 1 Gaucher disease. Similarly, it is not unusual for the CDER review divisions to accept for filing applications relying on historically controlled clinical trials. Examples of reproductive drug products for which a historical control is often relied on in the drug approval process include contraceptive drug products (e.g., most birth control pills, Mirena intrauterine device, NuvaRing (an intravaginal hormonal contraceptive), and Implanon (an implanted hormonal contraceptive)) and menopausal hormonal therapy products with the addition of a progestin to prevent endometrial cancer secondary to unopposed estrogen stimulation.

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[34] Id. at 27.

[35] We disagree with your statement that the sponsor's failure to identify precisely a historical control group is fatal to its claim that the trials supporting the approval of Mifeprex were historically controlled (Response to Opposition at 5-6). In situations where an investigational product is anticipated to have an effect that is readily discernible and greatly exceeds that which would be expected otherwise, the historical control may be relied upon without explicitly describing it as such. Examples of situations where this arises include, as here, the use of a drug for early medical abortion, given that the majority of pregnancies continue to term, and the use of a drug as a contraceptive, given that the pregnancy rate in sexually active women between 18 and 35 years old in the absence of contraception for one year is well documented at approximately 85% (Hatcher, RA, et al., 2012, Contraception Technology (20th ed.), Ardent Media, Inc., at 780.

You state that FDA did not conduct a statistical review of the results of the U.S. clinical trial (Petition at 29). The Agency, however, concluded that the clinical results of the supporting U.S. clinical trial were "similar enough to the results of the European studies" (the studies used to support the original approval of Mifeprex in Europe) that a statistical evaluation of the results of the U.S. trial was not required.[36]

You maintain that the Mifeprex approval is not in accordance with Agency guidance[37] on when only one effectiveness trial may be necessary for approval because: (1) mifepristone had not been approved for any use in any population in the United States and (2) no one had ever presented to FDA any evidence from adequate and well-controlled trials regarding any use for mifepristone.[38] As stated above, our approval of Mifeprex was based on not one but three studies that met the requirements of § 314.126. Therefore, Agency guidance concerning reliance on only one effectiveness trial is not relevant to the approval of Mifeprex.

You argue that FDA's acceptance of the French and U.S. clinical trial data violated § 314.126(e), which states that uncontrolled studies or partially controlled studies are not acceptable as the sole basis for approval of claims of effectiveness (Petition at 34-36). As explained above, the Mifeprex clinical trials were neither uncontrolled nor partially controlled. They were historically controlled, and the use of an historical control was appropriate under § 314.126(b)(2)(v). Consequently, § 314.126(e) is inapplicable.

Citing § 314.500, you contend that the approval of Mifeprex under subpart H was improper because FDA did not require the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone provides a meaningful therapeutic benefit over the standard method for terminating pregnancies (Petition at 37-40). You maintain that Mifeprex is the only drug that we have approved under § 314.520 (approval with restrictions to assure safe use) without requiring "that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials" (Petition at 37).

Nothing in subpart H requires that an applicant conduct comparative clinical trials in order to demonstrate that a drug product provides meaningful therapeutic benefit to patients over existing treatments. Furthermore, nothing in the concept of "meaningful therapeutic benefit" requires concurrent testing of a proposed drug with an existing treatment.[39] We have approved other drugs

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[36] FDA Memorandum to NDA 20-687 re: Statistical comments on Amendment 024, Feb. 14, 2000, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

[37] FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Effectiveness Guidance), available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[38] Petition at 31-32 (citing Effectiveness Guidance at 5-17).

[39] You state that "[c]onducting a concurrently-controlled randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable" (Petition at 32, note 145). You add that "[t]here are study designs that would have also allowed for blinding" (Id.). Assuming, arguendo, that it may have been feasible to design a randomized, concurrently-controlled study, such study was not required under our regulations; as described previously in this response, the clinical trials supporting the approval of Mifeprex

under subpart H based on clinical trials that do not directly compare the drug to an existing therapy, including Gleevec (imatinib mesylate), Tracleer (bosentan), and Xyrem (sodium oxybate). We also note that the latter two referenced drug products, Tracleer (bosentan) and Xyrem (sodium oxybate), were approved under the restricted distribution provisions at 21 CFR 314.520. As previously explained in this response, Mifeprex was deemed to have in effect an approved REMS under Title IX of FDAAA. The Mifeprex REMS, which was approved in June 2011 and is still in effect, incorporated the subpart H restrictions under which the drug was approved.

As evidenced by the foregoing, the studies supporting the 2000 approval of Mifeprex were consistent with the FD&C Act and FDA regulations, including § 314.126 and subpart H.

2. There Is No Need for an Audit of the French Clinical Data

You assert that FDA allowed "tainted data" to support the Mifeprex NDA by failing to require a comprehensive audit of the French clinical trial data after discovering violations of good clinical practices (Petition at 40-41). You maintain that we should therefore conduct a complete audit of all of the French clinical trial data to determine whether other trials must be conducted (Petition at 41 and 89).

We disagree with your characterization of both the French data and FDA's reliance on that data. You reference the Form FDA 483 issued on June 28, 2006, to Dr. Elisabeth Aubeny, as well as the Summary of Findings related to that Form FDA 483. It is not uncommon to have trial sites receive a Form FDA 483, listing the FDA investigator's observations regarding non-compliance with good clinical practice, at the conclusion of an inspection. The investigator will draft an Establishment Inspection Report (EIR) that reviews the violations noted and will recommend an action, taking into consideration the nature of the inspectional findings, any actions that occurred following the findings, and Agency policy. For products regulated by CDER, compliance reviewers in the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations (previously, the Division of Scientific Investigations) review the EIR, the Form FDA 483, and the evidence collected during the inspection, as well as any written response submitted timely by the inspected party, to determine whether the recommended action is appropriate and is supported by adequate evidence. This review evaluates each violation's effect on the timeliness, accuracy, and/or completeness of the data collected from the site to ascertain if the data are reliable. In this particular case, although there were violations cited on the Form FDA 483 and discussed in the EIR, the violations were determined not to affect the reliability of the data provided by that site. The statement you quote from the Summary of Findings reflects this conclusion. We note that, although the French studies were not performed under a U.S. investigational new drug application (IND), this is typical of many approved drugs that originally were developed or studied outside the United States, and is fully permissible under 21 CFR 312.120 (Foreign clinical studies not conducted under an IND) (including the version of the provision in effect at the time of the 2000

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were historically controlled, which was appropriate under § 314.126(b)(2)(v). Furthermore, your suggestion that there are study designs that would have allowed for blinding raises ethical issues that go beyond the scope of your Petition and this response.

approval of Mifeprex). FDA concluded that the French trials were conducted in accordance with good clinical practice,[40] and the Agency was able to validate the data from those studies.

It is worth noting that in 1996, when the Advisory Committee reviewed the French data without considering the U.S. data, the committee voted 6 to 2 that the French data alone demonstrated efficacy and 7 to 0 (with one abstention) that the French data supported safety.[41] The subsequent approval of Mifeprex was based not only on the data from the two French trials but also on the data from the large Phase 3 U.S. trial. The Advisory Committee received a report on the U.S. trial (the article by Spitz, et al., referenced in note 12 above) and had no comments.

For the foregoing reasons, there is no scientific or regulatory need for us to further review the French clinical data on Mifeprex.

3. Your Request for an Audit of the U.S. Clinical Data

In addition to your request that FDA conduct a full audit of the data from the French trials, you request that FDA conduct a full audit of all data from the U.S. trial (Petition at 1-2 and 89). Other than one footnote referring to a letter from the NDA sponsor to FDA (Petition at 89, note 384), you have provided no information supporting this request. Accordingly, we do not address this request further, other than to note that we do not believe there is any scientific or regulatory need to further review the U.S. clinical trial data relied on for approval of the Mifeprex NDA.

C. FDA Lawfully Approved Labeling for Mifeprex for Use with Misoprostol

You contend that FDA's "de facto" approval of misoprostol for use with Mifeprex as part of a medical abortion regimen was unlawful because the holder of the only approved NDA for misoprostol[42] did not submit a supplemental NDA for this new use (Petition at 41-45). You further

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[40] The regulations in effect at the time of the Mifeprex approval in 2000 refer to FDA accepting such studies when they are "well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community" FDA has generally interpreted that language as incorporating the principles of "good clinical practice" (see, e.g., ICH guidance for industry, *ICH E6 Good Clinical Practice: Consolidated Guidance* (E6 Guidance), available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm), which is the term used in the current regulations. The E6 Guidance states that GCP:

> is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that clinical trial data are credible

(E6 Guidance at 1).

[41] Mifeprex Approval Memorandum, supra note 16, at 1.

[42] Two abbreviated new drug applications (ANDAs) for misoprostol have been approved since Mifeprex was approved: ANDA 076095 (IVAX Pharmaceuticals, Inc., approved July 10, 2002) and ANDA 091667 (Novel Laboratories Inc., approved July 25, 2012).

argue that FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol by overseeing the creation of Mifeprex promotional materials that discuss the off-label use of misoprostol and by disseminating information about the off-label use in documents such as the press release announcing Mifeprex's approval (Petition at 46-47).

The approval of Mifeprex was based on evidence from three adequate and well-controlled clinical trials using the treatment regimen of administration of mifepristone on day one, followed approximately 48 hours later (i.e., on day three) by the administration of misoprostol (unless a complete abortion has already been confirmed before that time). Neither the FD&C Act nor FDA regulations require the submission of a supplemental NDA by the sponsor of the misoprostol NDA for the use of misoprostol as part of the approved treatment regimen for Mifeprex. In this situation, the "drug product" subject to section 505(b) of the FD&C Act (21 U.S.C. 355(d)) was Mifeprex.[43] The NDA for Mifeprex appropriately contained the full reports of investigations which have been conducted to show whether or not "such drug" is effective in use (§ 505(b)(1) of the FD&C Act), and FDA appropriately found that the Mifeprex NDA met the approval requirements in § 505(d) of the FD&C Act.

There are a number of drug products that FDA has approved as safe and effective in combination with another drug for a use that was not sought by the applicant of the second drug product, and for which the Agency did not require any change in the labeling of the second product (i.e., that the second product's labeling include the indication for use with the newly approved drug product). Examples of approved drug labeling that refer to the concomitant use of another drug without there being a specific reference to the combined therapy in the previously approved labeling for the referenced drug include the following:

- Xeloda (capecitabine) for treatment of metastatic breast cancer in combination with Taxotere (docetaxel) after failure of prior anthracycline-containing therapy[44]

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[43] In the Response to Opposition, you reference a July 2, 2002, letter submitted by the Population Council to Docket 01E-0363 re: Determination of Regulatory Review Period for Purposes of Patent Extension; Mifeprex (Response to Opposition at 12-13). In its July 2, 2002, letter, the Population Council made several statements regarding what it believed should be considered "the approved human drug product" for purposes of 21 CFR 60.22(a)(1), for purposes of patent term restoration. In the Agency's October 24, 2002, notice amending FDA's previous determination of the regulatory review period for Mifeprex (67 FR 65358), we addressed — and rejected — the Population Council's assertions. We stated that "[t]he applicant tries to characterize Mifeprex as mifepristone 'in combination with another active ingredient' in an attempt to take advantage of portions of the definition of 'human drug product' in 35 U.S.C 156(f), that is, a human drug product means 'the active ingredient of a new drug * * * as a single entity or in combination with another active ingredient.' The applicant points to the definition of 'combination product' at 21 CFR 3.2(e) in this effort. A more useful description of a drug 'in combination with another active ingredient' is found at 21 CFR 300.50 (two or more drugs combined in a single dosage form). Mifeprex is not mifepristone 'in combination with another active ingredient.' Mifeprex is single entity mifepristone" (67 FR 65358, note 2).

[44] We note your assertion that when Xeloda and Taxotere are used together, each is being used for an FDA-approved use (Response to Opposition at 11). Taxotere (docetaxel) was approved on May 14, 1996; its current labeling states that it is indicated as a single agent for treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy, and in combination with doxorubicin and cyclophosphamide as adjuvant treatment of patients with operable node-positive breast cancer. Xeloda (capecitabine), which

- Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin for *H. pylori* eradication
- Persantine (dipyridamole) as an adjunct to coumarin anticoagulants for prevention of postoperative thromboembolic complications of cardiac valve replacement
- Herceptin (trastuzumab) in combination with paclitaxel for treatment of metastatic breast cancer
- Vistide (cidofovir) administered with probenecid for treatment of CMV retinitis in patients with AIDS
- Daraprim (pyrimethamine) for treatment of toxoplasmosis when used conjointly with a sulfonamide

You maintain that the labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved and because it creates the false expectation that misoprostol is approved for medical abortion (Petition at 47). We disagree that the labeling for Mifeprex is misleading by virtue of the fact that it includes instructions for the use of misoprostol as part of the approved treatment regimen for Mifeprex. The Mifeprex labeling appropriately describes the clinical trial treatment regimen in which Mifeprex was shown to be safe and effective. The labeling for Mifeprex makes clear that Mifeprex tablets contain mifepristone, not misoprostol, and although the Indication and Usage section in the 2000 labeling does address the use of misoprostol in a regimen with Mifeprex, the labeling is clearly addressed to Mifeprex.

You claim that Mifeprex is misbranded because, per 21 CFR 201.6(a), the references to misoprostol in the Mifeprex labeling constitute a false or misleading representation that misoprostol itself is approved for medical termination of pregnancy (Petition at 48). In addition, you contend that Mifeprex is misbranded under section 502(j) of the FD&C Act (21 U.S.C. 352(j)) because it is unsafe when used as directed in the 2000 approved labeling (id.).

The references to misoprostol in the Mifeprex labeling do not render Mifeprex misbranded as described in § 201.6(a) because the labeling does not make any false or misleading representations with regard to misoprostol. We determined, and the labeling reflects, that Mifeprex is safe and effective for the termination of early pregnancy when used in combination with misoprostol. The approval was based on evidence from adequate and well controlled clinical trials in which misoprostol was administered two days after mifepristone to help stimulate uterine contractions; accordingly, the approved labeling describes the use of Mifeprex in combination with misoprostol.

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originally was approved on April 30, 1998, for the treatment of metastatic breast cancer that is resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, is currently approved (in addition to other indications) for use in combination with docetaxel for treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy. The indication to which this response refers is the concomitant use (i.e., use in combination) of the two drugs, a use that is not referenced in the labeling for Taxotere. Your arguments with respect to Actos (pioglitazone) in combination with a sulfonylurea, metformin, or insulin; Viread (tenofovir disproxil fumarate) in combination with other antiretroviral agents; and Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin (id.) are similarly inapposite.

Additionally, the approved labeling in no way implies that misoprostol alone would be safe and effective for the termination of pregnancy. Thus, the statements in the labeling are neither false nor misleading with regard to the use of misoprostol.

With regard to section 502(j) of the FD&C Act, Mifeprex is not misbranded under that provision because, as discussed in the following section, the approved regimen for Mifeprex is not "dangerous to health when used in the dosage or manner; or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof."

D. Mifeprex Is Safe for Its Approved Use and the Conditions of Approval Do Not Lack Essential Safeguards

You contend that FDA "approved mifepristone for use in a deregulated regimen that lacks key safeguards" (Petition at 5). You claim that in 2000, the Population Council repudiated distribution restrictions that it had proposed in 1996, and that FDA subsequently approved a regimen that does not embody restrictions sufficient to address legitimate safety concerns (Petition at 49). You note that the February 18, 2000, Mifeprex approvable letter stated that restrictions (per § 314.520) on the distribution and use of Mifeprex were needed to ensure safe use of the drug but that in March 2000, the Population Council said such restrictions were unwarranted (Petition at 51-52). You claim that we later yielded to the applicant on several important issues (Petition at 54-55).

FDA has found that Mifeprex is safe and effective for its intended use. It is true that, before the 2000 approval of Mifeprex, FDA and the applicant were not always in full agreement about the distribution restrictions. It is not unusual for such differences to emerge during the course of the review process for a proposed drug product. We ultimately determined that the distribution restrictions stated in the approval letter were appropriate to ensure the safety of Mifeprex for its intended use.[45] Three adequate and well-controlled clinical trials supported the safety of Mifeprex for its intended use, and over 15 years of postmarketing data and many comparative clinical trials in the United States and elsewhere continue to support the safety of this drug product.[46] Further, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Following is our response to the specific safety issues you raise in the Petition.

1. Ultrasound Dating

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[45] We note your reference in your Response to Opposition to the statement by the Reproductive Health Drugs Advisory Committee that it had concerns about the distribution proposal discussed at the July 19, 1996, meeting (Response to Opposition at 4 (referencing the minutes from the 1996 Reproductive Health Drugs Advisory Committee meeting)). In light of FDA's determination in 2000 that the distribution restrictions stated in the approval were appropriate to ensure that Mifeprex was safe for its intended use, as well as the 2011 approval of the Mifeprex REMS, the Committee's reservations in 1996 are not applicable.

[46] See, e.g., Raymond, EG, et al., 2013, First-Trimester Medical Abortion With Mifepristone 200 mg and Misoprostol: A Systematic review, Contraception, 87:26-37 In this article, 87 trials were reviewed and 91 references were cited.

You maintain that the Mifeprex regimen is unsafe because it does not require ultrasound examination. Specifically, you maintain that the use of transvaginal ultrasound is necessary to accurately date pregnancies and to identify ectopic pregnancies, and you note both that Mifeprex was approved in 2000 only for women through 49 days' gestation and that it is contraindicated for women with a confirmed or suspected ectopic pregnancy (Petition at 57-61).

Although the protocol for the U.S. clinical trial required a transvaginal sonogram (TVS) for each patient at Visit 1 and stated that the test should be used "as indicated" at Visits 2 and 3, this does not mean that a TVS is essential to ensure the safe use of Mifeprex.[47] As stated in the Mifeprex Approval Memorandum, during the review process, the Agency carefully considered the role of ultrasound.[48] In the clinical trials, ultrasound was performed to ensure proper data collection on gestational age, but in clinical practice, pregnancies can also be (and frequently are) dated using other clinical methods. (As discussed in section II.F below, safeguards employed during clinical trials are not always essential for safe use of the approved drug product.) As part of the restricted distribution of Mifeprex put in place in 2000, each provider must have the ability to accurately assess the duration of pregnancy and to diagnose ectopic pregnancy. We determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider.

You claim that the only way to date a pregnancy accurately enough to exclude EGA > 49 days is by using TVS (Petition at 58). That is incorrect. As noted above, using TVS (or any other method) does not ensure complete accuracy in dating a pregnancy. In most cases, a provider can accurately make such a determination by performing a pelvic examination and obtaining a careful history, which would include the following: date of last menstrual period, regularity of menses, intercourse history, contraceptive history, and (if available) home pregnancy test results.[49] If in doubt, the provider can order an ultrasound and/or a blood test measuring the quantitative beta-human chorionic gonadotropin (hCG) to further assist in dating the gestational age.

Furthermore, use of a TVS does not guarantee that an existing ectopic pregnancy will be identified. As of April 30, 2015, there were 89 unduplicated reports in FDA's Adverse Event Reporting System (FAERS) database of ectopic pregnancy in women in the United States who had received mifepristone for termination of pregnancy since the approval of Mifeprex in the United States. In

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[47] We note that the French clinical trials did not require an ultrasound examination; rather, the decision as to whether an ultrasound was needed was left to the discretion of the investigator.

[48] Mifeprex Approval Memorandum, supra note 16, at 5.

[49] See, e.g., Fielding, SL, et al., 2002, Clinicians' Perception of Sonogram Indication for Mifepristone Abortion up to 63 Days, Contraception, 66:27-31 (discussing the results of a prospective study of 1,016 women in a medical abortion trial at 15 sites that concluded that "clinicians correctly assessed gestational age as no more than 63 days in 87% of women. In only 1% (14/1013) of their assessments did clinicians underestimate gestational age. We conclude that the clinicians felt confident in not using ultrasound in most cases").

42.7% (38 of89) of the reported cases, an ultrasound was completed. Of the 38 cases that had an ultrasound completed, 55.3% (21 of 38) showed no changes indicative of ectopic pregnancy.[50] In light of the fact that Mifeprex is contraindicated for women with a confirmed or suspected ectopic pregnancy, we believe it is reasonable to expect that the women's providers would not have prescribed Mifeprex if a pelvic ultrasound examination had clearly indicated an ectopic pregnancy; this strongly suggests, therefore, that ultrasound examinations were falsely negative for ectopic pregnancy in these women. The currently approved labeling for Mifeprex reflects this, stating that the "presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex."[51]

2. Physician Training and Admitting Privileges

You contend that the administration of Mifeprex should have been restricted to physicians who have formal training in both pharmaceutical and surgical abortion and who have admitting privileges to emergency facilities (Petition at 62-65).

Although we did not restrict the administration of Mifeprex to physicians with the specific requirements you list in your Petition, we did conclude in 2000 that Mifeprex had to be provided by a physician who, among other qualifications, either (1) has the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or (2) has made plans to provide such care through other qualified providers and facilities.

During the clinical trials for Mifeprex, the principal investigators were trained in surgical abortions and were able to conduct any necessary surgical interventions.[52] The protocol for the U.S. trial was designed such that the studies were conducted at 17 centers where the principal investigators could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.

During the NDA review process, the issue of physician qualifications and certification was thoroughly discussed within the Agency, with the applicant, and with an outside consultant with expertise in early pregnancy termination. Although the distribution of Mifeprex was not restricted to any particular medical specialist, the Agency did determine in 2000 that certain restrictions were

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[50] Seventeen cases were identified as having an ultrasound with a possible ectopic pregnancy. Fourteen of these 17 (82.3%) cases noted appropriate follow-up procedures, such as additional hCG monitoring, ultrasounds, appointments, or emergency room referral, while two cases did not include any additional follow-up information. In the remaining case, a diagnosis of a heterotopic gestation (simultaneous ectopic pregnancy and intrauterine pregnancy) was noted.

[51] Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. .

[52] Additionally, it is common in drug development that the clinical investigators who conduct pivotal Phase 3 clinical trials have more specialized training than may be necessary to ensure the safe use of a drug post-approval. Examples are trials for male erectile dysfunction (typically conducted by urologists), hypertension (internists), depression (psychiatrists), and endometriosis (gynecologists).

necessary under § 314.520. In accordance with this determination, the Prescriber's Agreement for Mifeprex stated the following:[53]

> Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:
>
> - Ability to assess the duration of pregnancy accurately.
> - Ability to diagnose ectopic pregnancies.
> - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have [sic] made plans to provide such care through others, and are [sic] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
> - Has read and understood the prescribing information of Mifeprex….

As noted in the Mifeprex Approval Memorandum, the requirement that a physician certify, by signing the Prescriber Agreement, that he or she has the qualifications described in that Agreement limited the physicians who would be eligible to receive Mifeprex from the sponsor to those who are familiar with managing early pregnancies.[54] Because only such qualified physicians would be using or would oversee the use of Mifeprex, we concluded that there was no need for special certification programs or additional restrictions. Additionally, as noted in the Mifeprex Approval Memorandum, in the U.S. clinical trial of Mifeprex, 11 out of roughly 850 patients needed surgical intervention to treat bleeding, and three of these patients were treated by non-principal investigators such as emergency room physicians and a non-study gynecologist.[55] These data suggested that patients would receive any needed surgical intervention from either their physician or another physician with the needed skills.[56] The Mifeprex Approval Memorandum also pointed out that the Mifeprex labeling and the Medication Guide approved at that time highlight that surgery may be needed and that patients must understand whether the provider will furnish any necessary medical intervention or whether they will be referred to another provider and/or facility.[57]

In addition, one of the Phase 4 commitments accompanying the approval of Mifeprex was a cohort-based study of safety outcomes when Mifeprex is prescribed by physicians with the skills for surgical intervention compared to physicians who refer patients for surgical intervention. In a February 2008 submission, the applicant stated that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful

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[53] Mifeprex labeling (June 8, 2011), Mifeprex (mifepristone) tablets, 200 mg, Prescriber's Agreement, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020687s014lbl.pdf.

[54] Mifeprex Approval Memorandum, supra note 16, at 5.

[55] Id.

[56] Id.

[57] Id.

study to assess this specific issue. After review of this submission, the Agency: (1) concurred with the applicant regarding the non-feasibility of conducting a meaningful study and (2) concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. Accordingly, on September 26, 2008, the Agency released the applicant from this commitment.

The provisions of the currently approved labeling (including the REMS) that relate to provider training and admitting privileges are substantially similar to the labeling provisions approved in 2000. Under current labeling, healthcare providers who administer Mifeprex must be licensed to prescribe, and must have the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also (1) be able to provide any necessary surgical intervention, or (2) have made arrangements for others to provide for such care. Healthcare providers must be able to ensure that women have access to medical facilities for emergency care, and must agree to other responsibilities, including reviewing and signing the Patient Agreement Form with the patient and providing each patient with a copy of the signed Patient Agreement Form and the Medication Guide.[58]

3. "Dear Health Care Provider" Letter and FDA "Mifepristone Questions and Answers"; Adverse Events Discussed in Response to Opposition

You maintain that your concerns about the safety of Mifeprex are validated by the April 19, 2002, "Dear Health Care Provider" letter issued by Danco and by statements in the "Mifepristone Questions and Answers" (Mifepristone Q&A) document (placed on FDA's Web site on April 17, 2002) about reports of serious adverse events, including ruptured ectopic pregnancies and serious systemic bacterial infections (Petition at 65-71). You argue that FDA understated the possibility that the Mifeprex regimen caused the serious adverse events referred to in the letter and inappropriately attempted to link those events to the unapproved vaginal administration of misoprostol (Petition at 67-68).

The fact that Danco and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 (or that a subsequent Dear Health Care Provider letter and a Dear Emergency Room Director letter were issued on September 30, 2004) does not imply that the approved Mifeprex regimen is unsafe. It is not uncommon for drug sponsors to issue "Dear Health Care Provider" letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, "[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely."[59] The intent of the two "Dear Health Care Provider" letters and the "Dear Emergency Room Director" letter was to provide health care personnel with new safety information regarding the use of Mifeprex. Similarly, when these letters were issued, we posted Mifepristone Q&A documents to

[58] Mifeprex REMS, available at http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=35

[59] See Historical Information on Mifepristone (Marketed as Mifeprex), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm.

address questions that might arise as a result of the issuance of the letters. We disagree that we have in any way "inappropriately attempted to link" the adverse events to the intravaginal use of misoprostol. Rather, the April 2002 Mifepristone Q&A document accurately stated that in all of the adverse event cases at that time,[60] the misoprostol was given vaginally not orally; that we did not know what role, if any, the use of Mifeprex and vaginal misoprostol may have in the development of serious infections; and that FDA had not reviewed data on the safety and effectiveness of vaginal administration of misoprostol.

You maintain that it is particularly important for FDA to respond to these adverse events because the clinical trials in support of Mifeprex allegedly did not adhere to the Agency's scientific methodology for such trials (Petition at 70). As explained above, however, the clinical trials supporting the approval of Mifeprex were adequate and well-controlled, and they provided substantial evidence of the safety and effectiveness of the drug product in accordance with the FD&C Act and FDA regulations.

In your Response to Opposition, you state that the serious adverse events reported to date are consistent with concerns expressed before approval (Response to Opposition at 16). You refer to the death of Holly Patterson on September 17, 2003, after she had taken Mifeprex and misoprostol to terminate her pregnancy. You state that Ms. Patterson's apparent death from a serious systemic bacterial infection after taking Mifeprex is "not the first such death since FDA approved Mifeprex," referring to a fatality due to serious systemic bacterial infection mentioned in the April 2002 "Dear Health Care Provider Letter" (Response to Opposition at 16-17). You also question whether adverse events for Mifeprex will be adequately reported to FDA (Response to Opposition at 18).

As with all approved drug products, we continue to monitor the safety of Mifeprex. Since the approval of Mifeprex, the Agency has issued two public health advisories (one in July 2005[61] and one in March 2006[62]) and posted multiple MedWatch safety alerts (in November 2004[63] and July 2005, the latter with updates in November 2005 and March 2006[64]). As referenced above, Danco has issued two Dear Health Care Provider letters and one Dear Emergency Room Director letter. Furthermore, since you submitted your Response to Opposition, Danco has revised the labeling for

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[60] The April 2002 Mifepristone Q&A document refers to cases of ectopic pregnancy, sepsis, and heart attack.

[61] Available at, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051734.htm.

[62] Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051196.htm.

[63] Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166463.htm.

[64] Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111339.htm.

Mifeprex (including the prescribing information, the Medication Guide, and the Patient Agreement), in November 2004, December 2004, July 2005, and April 2009[65] to provide prescribers and women with additional information about infection, vaginal bleeding, and ectopic pregnancy.

The boxed warning for Mifeprex currently states the following:

> Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.
>
> • Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis.
>
> • Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding.
>
> Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MIFEPREX REMS Program.
>
> Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol.
>
> Advise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe MIFEPREX, so that the provider knows that she is undergoing a medical abortion.

[65] The Mifeprex labeling also was revised in June 2011 when the REMS was approved. In addition, as described above, FDA is today approving a supplemental NDA submitted by Danco that proposed modified labeling for Mifeprex. See Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

The WARNINGS section of the Mifeprex labeling states, in part, the following:

[With respect to infection and sepsis:]

> As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.
>
> A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

[With respect to uterine bleeding:]

> Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.
>
> Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.
>
> Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in women who bleed heavily.
>
> Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfu¬sions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to $\leq 0.1\%$ of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

[With respect to ectopic pregnancy:]

> MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.
>
> Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

The Agency has regularly completed a cumulative summary of U.S. postmarketing adverse events reported for the use of mifepristone for medical termination of pregnancy. From the approval date of Mifeprex (September 28, 2000) through October 31, 2012, we received 2,740 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy,[66] including 57 reports of severe infections[67] and 416 incidences of blood loss requiring transfusion. From November 1, 2012, through April 30, 2015, we received 984 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy, including 9 reports of severe bacterial infections and 134 incidences of blood loss requiring transfusion.[68] As of April 30, 2015, 89 ectopic pregnancies associated with the use of mifepristone in the United States had been reported since the approval of Mifeprex. As of July 24, 2015, 17 U.S. deaths had been reported since the approval of Mifeprex. Deaths were associated with sepsis in 8 of the 17 reported fatalities (7 cases tested positive for *Clostridium sordellii*, and 1 case tested positive for *Clostridium perfringens*).[69] Seven of the eight fatal sepsis case reported vaginal misoprostol use;

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[66] This represents data from the FDA's previous adverse event reporting system, which was known as AERS.

[67] Severe infections generally involve death or hospitalization for at least 2-3 days, intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, and any other physical or clinical findings, laboratory data or surgery that suggest a severe infection.

[68] This represents data from the current FDA Adverse Event Reporting System (FAERS), which was implemented in September 2012 and replaced AERS. FDA migrated all of the data from the previous reporting system (AERS) to FAERS. FDA validated and recoded product information as the reports from the AERS database were migrated to the FAERS database. In addition, the FAERS database features a new search functionality that is based on the date FDA initially received for the case; this facilitates more accurate follow-up for cases that have multiple reports and multiple receipt dates. For these reasons, there may be differences in the case counts between AERS and FAERS.

[69] We note your statements in your October 10, 2003, Response to Opposition Comments that the presence of retained products of conception can lead to the development of intrauterine or systemic infection and that Mifeprex might potentiate this possibility through negative effects on immune system function or normal protective mechanisms (Response to Opposition at 17). Regarding retained products of conception and the emergence of infections, based on autopsy and/or ultrasound reports, there were no retained products of conception in any of the eight deaths associated with infections (sepsis). With respect to your claim that Mifeprex might increase the likelihood of infection by adversely affecting immune system function, although

one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a delayed onset of toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. In the ninth case, infection was ruled out and the final autopsy report listed pulmonary emphysema as the cause of death. [70]

We disagree with your assertion that adverse event reporting for Mifeprex is "spotty" and that, as a result, the database for post-approval adverse events for Mifeprex is incomplete (Response to Opposition at 18). You are correct that reporting to the Agency's MedWatch program is voluntary, and we acknowledge that there is always a possibility with any drug that some adverse events are not being reported. We believe, however, that the potential for underreporting of serious adverse events associated with the use of Mifeprex for medical abortion has been very low because of the restricted distribution of the product and because healthcare providers have agreed in writing to report any hospitalizations, transfusions, or other serious adverse events associated with the drug to the sponsor, which is required under FDA's regulations to report all adverse events, including serious adverse events, to the Agency (see 21 CFR 314.80, 314.81). As with all drugs, we will continue to closely monitor the postmarketing safety data on Mifeprex.

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published experimental data from animal models suggest that this is a theoretical possibility, the overall event rate of serious infections does not support this. If Mifeprex were adversely affecting immune system function, we would expect to see a much higher rate of serious infections from more common organisms, as well as a higher number of deaths in Europe (where mifepristone has been approved for over 24 years) and in the United States. Contrary to your statements, data from the medical literature and findings by the CDC suggest that the critical risk factor in the reported cases of sepsis is pregnancy itself (see Miech, RP, 2005, Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium sordellii*, Ann Pharmacother, 39:1483-1488). In May 2006, FDA, along with the CDC and the National Institute of Allergy and Infectious Diseases at the National Institutes of Health held a workshop on emerging clostridial disease. The issue of immunosuppression also was discussed at length during this public workshop. It was clear from the presentations at the workshop that *C. sordellii* causes rapid and serious clinical illness in settings other than medical abortion, including among pregnant women who have recently undergone spontaneous abortion or term delivery. The fact that cases of *C. sordellii* have been identified both in pregnant women who have undergone medical abortion and those who have not supports the idea that the physiology of pregnancy may be a more plausible risk factor for *C. sordellii* illness than having undergone a medical abortion with Mifeprex.

[70] FDA is aware of 11 additional deaths of women in foreign countries who used mifepristone for the termination of pregnancy. This included one death associated with sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial, and 10 deaths identified from post-marketing data. These 10 fatal cases were associated with the following: sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure"; thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes a jejunostomy feeding tube, and severe cystic fibrosis; *Clostridium septicum* sepsis (from a published literature report).

E. Withdrawal of the Approval for Mifeprex Based on Current Use Is Not Appropriate

You claim that Mifeprex abortion providers have disregarded the restrictions in the approved regimen "without any reaction from FDA, the Population Council, or Danco" (Petition at 71). You also claim that "common departures from the approved regimen" have included (1) offering the regimen to women with pregnancies beyond 7 weeks and (2) eliminating the second of the three prescribed visits to the health care provider (Petition at 72-74). You argue that we should withdraw approval of Mifeprex under § 314.530(a)(4) due to the failure of the Population Council and Danco to adhere to the postmarketing restrictions in the approval letter (Petition at 71).

In the Response to Opposition, you suggest that some providers have not met their obligations because many prescriber Web sites (1) advertise the Mifeprex regimen as being available for patients whose pregnancies have progressed beyond 49 days and (2) indicate that patients take misoprostol at home rather than at the provider's office (Response to Opposition at 19-20). Thus, you maintain that many prescribers have allowed patients to make false statements and that the applicant is obligated to stop sales to these prescribers (id. at 20). You claim that prescribers have disregarded the requirements imposed with the 2000 approval of Mifeprex to provide patients with the Medication Guide, obtain their signatures on the Patient Agreement, and give them the opportunity to read and discuss these documents (id. at 20-21). You state that because some prescribers, with the applicant's tacit approval, have permitted patients to sign the Patient Agreement while effectively directing them not to adhere to its requirements, the applicant cannot be described as meeting its obligations (id. at 21).

FDA is aware that medical practitioners may use modified regimens for administering Mifeprex and misoprostol. However, FDA does not believe that it is appropriate to initiate proceedings under 21 CFR 314.530 or section 505(e) of the FD&C Act to withdraw the approval of Mifeprex based on available information regarding the distribution of Mifeprex.

The Mifeprex approval letter included nine items that the applicant and/or prescriber were obligated to follow. As stated earlier in this response, Mifeprex has been subject to a REMS which incorporated these restrictions, including by appending a Prescriber's Agreement outlining required qualifications and guidelines prescribers must agree to follow. Specifically, the Prescriber's Agreement required each physician to attest to possessing certain necessary skills and abilities related to managing early pregnancy to ensure safe use of the drug.[71] The Prescriber's Agreement also contained responsibilities that prescribers must carry out.[72] The Prescriber's Agreement stated that prescribers must have read and understood the prescribing materials.[73]

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[71] Prescriber's Agreement, supra note 53, at 1.

[72] Id. at 1-2.

[73] Id. at 1.

The 2000 Prescriber's Agreement also required that the prescriber (1) provide each patient with a copy of the Medication Guide and the Patient Agreement, (2) fully explain the procedure to the patient, and (3) give the patient the opportunity to read and discuss the Medication Guide and Patient Agreement.[74] The Medication Guide and the Patient Agreement stated the approved dosage and administration of Mifeprex. FDA has no evidence, nor have you provided any evidence, that prescribers have not signed the Prescriber's Agreement, or that women either have not been given the opportunity to read and discuss the Patient Agreement or have not signed the Patient Agreement.

As noted above, restrictions on the distribution and use of Mifeprex substantially similar to those approved in 2000 remain in place today.

F. Safeguards Employed in Clinical Trials Are Not Necessarily Essential Conditions for Approval

You maintain that we effectively approved a drug regimen that we had not tested because the Mifeprex regimen approved in 2000 does not include important safeguards employed in the U.S. clinical trial (e.g., governing physician training, use of ultrasound, 4-hour post-misoprostol monitoring, physician privileges at facilities that provide emergency care) (Petition at 75-76). You argue that we should not have extrapolated conclusions about the safety and effectiveness of the Mifeprex regimen from data generated under trial conditions that do not mirror the approved regimen (id.).

We disagree with your assertions. Furthermore, your implication that the approved conditions of use for a drug product must mirror those used in the clinical trials supporting its approval is incorrect. As discussed above with respect to ultrasound dating and physician qualifications, safeguards employed in clinical trials are often not reflected in approved drug product labeling nor are they necessarily needed for the safe and effective use of the drug product after approval. Many clinical trial designs are more restrictive (e.g., additional laboratory and clinical monitoring, stricter inclusion and exclusion criteria, more visits) than will be necessary or recommended in postapproval clinical use; this additional level of caution is exercised until the safety and efficacy of the product is demonstrated. For example, in menopause hormonal therapy trials, specialists perform periodic endometrial biopsies to establish the safety of long-term hormone use. Once the safety of the product has been established, these biopsies are not recommended in the approved product labeling, nor are they routinely performed in actual use with the approved product. During our review of the clinical data submitted in support of an NDA, we make an assessment of the procedures employed during the clinical trials and the conditions under which the drug was studied. This assessment is reflected in the approved labeling for the drug product.

Upon reviewing the data submitted in support of the Mifeprex NDA, we concluded in 2000 that restrictions requiring ultrasound dating of gestational age of the pregnancy and limiting access to Mifeprex to physicians trained in surgical abortions and capable of performing surgical intervention if complications arise subsequent to use of Mifeprex were not necessary to ensure its safe use (see discussion in section II.D above).

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[74] Id.

G. FDA Appropriately Concluded That Studies of Mifeprex in Pediatric Patients Were Unnecessary

You maintain that our 2000 approval of Mifeprex violated regulations requiring that new drugs be tested for safety and effectiveness in the pediatric population (Petition at 76). You state that although we stated in the September 28, 2000, approval letter that the application was subject to the Pediatric Rule (21 CFR 314.55), we waived the requirement without explanation (Petition at 78). You contend that the Mifeprex application was not in accordance with any of the three provisions under which an applicant may obtain a waiver under 21 CFR 314.55(c)(2) of the pediatric study requirement, for the following reasons:

- 21 CFR 314.55(c)(2)(i) does not apply because FDA maintained that Mifeprex represented a meaningful therapeutic benefit over existing treatments and because Mifeprex can be expected to be used in a substantial number of pediatric patients.

- 21 CFR 314.55(c)(2)(ii) does not apply because pediatric studies of Mifeprex would not have been either impossible or highly impractical because a large population of pediatric females becomes pregnant each year and the female population is evenly distributed throughout the country.

- 21 CFR 314.55(c)(2)(iii) does not apply because FDA stated that there was no reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen than older females (Petition at 79-82).

As an initial matter, we reject your contention that the Population Council did not provide evidence from any adequate and well-controlled adult studies of Mifeprex, and that therefore it was inappropriate to rely on the submitted adult studies under § 314.55(a) with respect to the use of Mifeprex in the pediatric population (Petition at 82). As discussed above, the Mifeprex approval was based on three adequate and well-controlled clinical trials.

Our conclusion that studies of Mifeprex in pediatric patients were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time.[75] We determined that there were sufficient data from studies of mifepristone. Therefore, the Mifeprex approval letter should have stated our conclusion that the pediatric study requirements were waived for pre-menarchal patients and that the pediatric study requirements were met for post-menarchal pediatric patients, rather than stating that we were waiving the requirements for all pediatric age groups.[76]

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[75] FDA was enjoined from enforcing 21 CFR § 314.55 under *Ass'n of Am. Physicians& Surgeons v. FDA*, 226 F. Supp. 204 (D.D.C. 2002). However, on December 3, 2003, the President signed into law the Pediatric Research Equity Act of 2003 (PREA 2003), Public Law 108-155, which gave FDA the statutory authority to require pediatric studies of drugs when such studies are needed to ensure the safe and effective use of drugs in children. PREA 2003 stated that any waivers or deferrals that were granted under the Pediatric Rule were considered to be granted under PREA 2003 (see Section 4 of Public Law 108-155).

[76] FDA's implementation of the Pediatric Rule was still at a relatively early stage in September 2000 and the Agency was not always precise regarding the language used in approval letters to distinguish between situations where studies were waived and where studies were not needed because the requirements were met.

It is still our scientific opinion, based on the medical literature and over 15 years of use in the United States, that there is no biological reason to expect menstruating females under age 18 — compared to women age 18 and older — to have a different physiological outcome with the Mifeprex regimen.[77]

H. The Mifeprex Approval Letter Included Appropriate Phase 4 Commitments

You state that although the Population Council agreed in 1996 to perform Phase 4 studies with six different objectives, the Mifeprex approval letter included only two Phase 4 study obligations (Petition at 85-86). You allege that the changes in its Phase 4 commitments were largely in response to the Population Council's unwillingness to explore the "ramifications" of the Mifeprex regimen (Petition at 87). You maintain that this alleged "curtailment" of Phase 4 study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (Petition at 88).[78]

We disagree with your assertions. Our process for determining the appropriate Phase 4 studies for Mifeprex adequately addressed our concerns and reflected typical Agency-applicant interactions to reach consensus on appropriate postmarketing studies.[79] It is common for proposed Phase 4 commitments to evolve during the application review process. As you note (Petition at 85), in 1996, the Population Council committed to six postmarketing studies with the following objectives:

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[77] In the Mifeprex Approval Memorandum, the Office Director stated, "FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients" (Mifeprex Approval Memorandum, supra note 16, at 7).

[78] We note that post-marketing studies are not required for approvals under 21 CFR 314.520.

[79] You also state that, "[a]s a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects" (Petition at 84). This argument is not relevant to Mifeprex, which is approved for medical termination of pregnancy. Mifeprex is not approved for long-term or chronic use, which is an important factor in assessing the need to study long-term effects of a drug. Long-term safety for a single-dose medication is generally not a concern. However, FDA routinely monitors postmarketing safety data for all approved drugs. Mifeprex is no exception. FDA's Office of Surveillance and Epidemiology continuously monitors available safety data from use of mifepristone for termination of pregnancy both within and outside of the United States and has not identified any long-term safety signals. The Mifeprex adverse events reported are consistent with product labeling and with what can be expected with spontaneous and surgical abortions. Furthermore, as explained in this response, since Mifeprex's approval, safety concerns and adverse events have been monitored through enhanced surveillance and reporting by certified prescribers, and we have required a REMS for Mifeprex including a Medication Guide, elements to assure safe use, an implementation system that requires the sponsor to assess the performance of certified distributors, and a timetable for submission of assessments of the REMS. We also continue to closely monitor the post-marketing safety of mifepristone for termination of pregnancy for any new or long-term signals.

(1) Monitor the adequacy of the distribution and credentialing system.

(2) Follow-up on the outcome of a representative sample of Mifeprex-treated women who have surgical abortion because of method failure.

(3) Assess the long-term effects of multiple use of the regimen.

(4) Ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

(5) Study the safety and efficacy of the regimen in women under age 18, women over age 35, and women who smoke.

(6) Ascertain the effect of the regimen on children born after treatment failure.

As stated in the Mifeprex Approval Memorandum (at 7), during the final review of the Mifeprex NDA in 2000, items 1, 2, 4, and 5 above were revised and integrated into a single Phase 4 study to assess whether, for providers who did not have surgical intervention skills and referred patients for surgery, clinical outcomes were similar to those of patients under the care of physicians (such as those in the clinical trials) who possessed surgical skills. Based on a revised protocol, this Phase 4 study would monitor the adequacy of provider qualifications (item 1) and collect data on safety outcomes and method failures (item 2) and return of patients for their follow-up visits (item 4). Because patients would not be restricted to a specific age range or smoking status, information to address item 5 also would be obtained. In a second Phase 4 study, the applicant would examine the outcomes of ongoing pregnancies (i.e., method failures) through a surveillance, reporting, and tracking system (item 6). Thus, although the approval letter listed only two Phase 4 studies, those two studies incorporated all but one element of the six studies listed in the September 18, 1996, approvable letter concerning the Mifeprex NDA. (As discussed below, the remaining study was not included for logistical and practical reasons.)

As mentioned in section II.D.2 above, for the first Phase 4 study, which addressed items 1, 2, 4, and 5 above, the applicant reported in a submission in February 2008 that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful study to assess this specific issue. We agreed with the applicant regarding the non-feasibility of conducting a meaningful study and concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. In September 2008, we released the applicant from this postmarketing commitment.

For the second Phase 4 study, which addressed item 6 above, based on the reporting of ongoing pregnancies during the first 5 years of Mifeprex distribution, the applicant provided updates in January 2006 and November 2007. Danco reported that only one to two pregnancies per year were followed for final outcomes, and explained that the small number was due, in part, to the requirement that the patients consent to participation after seeking a pregnancy termination. In January 2008, because of the lack of an adequate number of enrolled women, and based on subsequent reports, we released the applicant from this postmarketing commitment.

In addition, as noted in the Mifeprex Approval Memorandum (at 7), we agreed with the Population Council both that it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug and that the pharmacology of mifepristone does not suggest any carryover effect after one-time administration. Accordingly, we did not include item 3 as a Phase 4 commitment in the September 28, 2000, approval letter. However, we note that data from many other studies reported in the medical literature using mifepristone for, e.g., fibroids, uterine myoma, meningioma, psychiatric illnesses, and Cushing's disease, in much higher daily and lower daily doses for chronic use (months) have not raised any major safety issues.[80]

III. REQUEST FOR STAY AND REVOCATION OF APPROVAL

You request that we immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on your Petition (Petition at 2). You cite 21 CFR 10.35 as the basis for your request for a stay (Petition at 1). In addition, you urge us to revoke the approval of Mifeprex because of the purported legal violations and safety concerns set forth in your Petition (Petition at 2).

As described above, we are denying your Petition. Therefore, your request for a stay pending final action on your Petition is moot.

For the reasons set forth in section II of this response, we conclude that you have not presented any evidence that the applicable grounds in 21 CFR 314.530 have been met with respect to Mifeprex. Furthermore, you have not provided any evidence that any of the applicable grounds in section 505(e) of the FD&C Act have been met for Mifeprex.[81] Therefore, you have not provided any evidence that would serve as a basis for seeking to withdraw the approval of Mifeprex.

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[80] See, e.g., Tristan, M, et al., 2012, Mifepristone for Uterine Fibroids (Review), Cochrane Library, 8:1-47; Esteve, JL, et al, 2013, Mifepristone Versus Placebo To Treat Uterine Myoma: A Double-Blind, Randomized Clinical Trial, Int J Womens Health, 5:361; Spitz, IM, et al., 2005, Management of Patients Receiving Long-Term Treatment With Mifepristone, Fertil Steril, 84:1719; Blasey, CM, TS Block, JK Belanoff, and RL Roe, 2011, Efficacy and Safety of Mifepristone for the Treatment of Psychotic Depression, J Clin Psychopharmacol, 31:436; Fleseriu, M, et al., 2012, Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome, J Clin Endocrinol Metab, 97:2039.

[81] You have not presented any clinical data or other information demonstrating that Mifeprex is unsafe for use under its approved conditions for use, either on the basis of evidence available to the Agency at the time of approval or when also considering evidence obtained subsequent to approval. In addition, you have not provided any new evidence that, when evaluated with the evidence available at the time of Mifeprex's approval, shows that there is a lack of substantial evidence that the drug will have its intended effect.

Docket No. FDA-2002-P-0364

IV. CONCLUSION

We appreciate and share your concerns about the need to appropriately manage the risks associated with the use of Mifeprex. Our concerns about the potential complications associated with Mifeprex led to its approval in accordance with 21 CFR 314.520. It was deemed to have in effect a REMS in 2007, and it has had an approved REMS since 2011.[82]

For the reasons set forth above, your request that we immediately stay the approval of Mifeprex is moot, and we deny your request that we revoke approval of the Mifeprex NDA. In addition, we deny your request that we conduct an audit of all records of the French and U.S. clinical trials supporting the Mifeprex approval. As with all approved new drug products, we will continue to monitor the safety of Mifeprex and take any appropriate actions.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[82] As of today's approval of Danco's supplemental NDA, the Medication Guide is no longer part of the REMS. However, the Medication Guide will remain as part of approved patient labeling and will be required to be provided to the patient under current Medication Guide regulations.

No. 23-10362

IN THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

ALLIANCE FOR HIPPOCRATIC MEDICINE; AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS; AMERICAN COLLEGE OF PEDIATRICIANS; CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS; SHAUN JESTER, D.O.; REGINA FROST-CLARK, M.D.; TYLER JOHNSON, D.O.; GEORGE DELGADO, M.D.,

Plaintiffs-Appellees,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, Commissioner of Food and Drugs; JANET WOODCOOK, M.D., in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration; PATRIZIA CAVAZZONI, M.D., in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, Secretary, U.S. Department of Health and Human Services,

Defendants-Appellants,

DANCO LABORATORIES, L.L.C.,

Intervenor-Appellant.

ADDENDUM TO EMERGENCY MOTION FOR A STAY PENDING APPEAL

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December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

(1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:

- Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.

- Dosage and Administration:
  - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

  - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
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- Contraindications - Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

- Adverse Event Reporting - Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

- Additional studies - The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

(2) Retain the Mifeprex REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Mifeprex

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H), "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.[1]

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[2] Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use included: (1) prescriber certification (ETASU A); (2) that Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber

[1] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.
[2] 73 FR 16313 (Mar. 27, 2008).

(ETASU C); and (3) that Mifeprex is dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the applicant Danco Laboratories, LLC (S-020 efficacy supplement). The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective, as well as the process for follow-up after administration of the drug.

Specifically, the following changes, among others, were made as part of the 2016 approval:[3]

- Revised the dosing regimen to consist of 200 mg of Mifeprex taken by mouth, followed in 24-48 hours by 800 mcg of misoprostol taken buccally (in the cheek pouch). This differs from the originally approved dosing regimen of 600 mg of oral Mifeprex followed 48 hours later by 400 mcg of oral misoprostol.

- Revised the indication for use of Mifeprex, in a regimen with misoprostol, to extend the maximum gestational age for the medical termination of intrauterine pregnancy from 49 days to 70 days.

- Reduced the number of office visits by the patient under the approved regimen from three to one.

- Replaced the term "physician" with the term "healthcare provider."

In addition, after reviewing the data and information submitted by the applicant in the S-020 efficacy supplement, and after taking into consideration the safety data that had become available since the initial approval of Mifeprex in 2000, we determined the Mifeprex REMS continued to be necessary to ensure the benefits of the product outweigh the risks. However, we approved modifications to the Mifeprex REMS that reflected the changes approved in the efficacy supplement. These changes to the REMS included, among others:[4]

- Updating the Prescriber Agreement Form to reflect the revised indication and dosing regimen.

- Removing the Medication Guide as a REMS element (but retaining the Medication Guide as labeling).

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[3] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

[4] See https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf.

- Removing the requirement that certified prescribers report certain enumerated adverse events to the applicant (specifically, any hospitalization, transfusion or other serious adverse events), but retaining the requirement that certified prescribers report all deaths to the sponsor.

Under the March 2016 approval, the Mifeprex REMS also continued to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.[5]

B. Generic Version of Mifeprex

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). This action took place after this Petition was submitted to the Agency. As required by 21 CFR 314.94(a)(8), GenBioPro's approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex. Accordingly, although we refer to the Mifeprex labeling in several sections of this response, our discussions in this response apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.[6]

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. -1(i)). At the time we approved GenBioPro's generic version of Mifeprex, that ANDA product was required to use a single, shared system for the ETASU with the brand drug product, Mifeprex, unless the requirement was waived by FDA (21 U.S.C. 355-1(i)). FDA did not waive this requirement. Accordingly, at the same time that FDA approved GenBioPro's generic version of Mifeprex in 2019, FDA approved a supplemental new drug application (sNDA) for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In establishing the single, shared system REMS in 2019, no substantive changes were made to the ETASU in the March 2016 Mifeprex REMS. References to the REMS in this response refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

C. In-Person Dispensing Requirement During the COVID-19 PHE

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[5] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf.

[6] We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone - as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

FDA has recognized that during the COVID-19[7] public health emergency (PHE),[8] certain REMS requirements for various products may be difficult to comply with because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. The Agency has also received queries concerning products with REMS that have ETASUs, including REMS with ETASUs that restrict distribution, and the impact of such ETASUs on patient access when patients self-isolate or are subject to quarantine.

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 PHE regarding the requirement in the Mifepristone REMS Program that mifepristone used for medical termination of intrauterine pregnancy through 70 days gestation be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement").

Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020 to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[9]

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

FDA's intent to exercise enforcement discretion with respect to these requirements during the COVID-19 PHE was the result of a thorough scientific review by experts within FDA's Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports.

D. Minor Modification

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[7] The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19).

[8] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[9] *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

In response to a request submitted by the applicants, FDA approved a minor modification to the Mifepristone REMS Program on May 14, 2021. This minor modification revised the Patient Agreement Form to use gender neutral language. Specifically, the pronouns "she" and "her" in the Patient Agreement Form were replaced with "the patient." The minor modification also included revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form. These changes did not affect the substance of the Patient Agreement Form, the REMS document, or the Mifepristone REMS Program.

E. Review of the Mifepristone REMS Program

In 2021, FDA also undertook a full review of the Mifepristone REMS Program.[10] In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA (together, the Applicants). As discussed in more detail below, based on our review of this information, FDA has determined that certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation; and therefore, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risk. Specifically, we find that the healthcare provider certification and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions continue to be necessary components of the REMS to ensure the benefits of mifepristone outweigh the risks for this indication.

We also find that the in-person dispensing requirement is no longer necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation. We have concluded that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added.[11] Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Accordingly, today we are sending a REMS Modification Notification letter to both Applicants in the Mifepristone REMS Program. As stated in that letter, FDA has concluded that a modification is necessary and must include the following changes:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

[10] We note that the Agency is in litigation regarding the Mifepristone REMS Program and committed to conducting a full review of the Mifepristone REMS Program, including reviewing any relevant data and evidence submitted to the Agency by the Plaintiffs in that litigation (*Chelius et al v. Becerra*, Joint Mot. to Stay Case Pending Agency Review, ECF No. 148, May 7, 2021, Civ. No. 1:17-00493 (D. Haw.)).

[11] Although we have determined that the Mifepristone REMS Program must be modified to add a requirement for pharmacy certification, this was not raised in your Petition and therefore is not discussed further in this response.

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- Adding a requirement that pharmacies that dispense the drug be specially certified.

II. DISCUSSION OF ISSUES RAISED

A. Mifeprex Regimen

1. Indications and Usage

In the Petition, you ask FDA to restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to limit Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, to 49 days gestation (Petition at 1 and 3). For the reasons explained below, we deny this request.

Citing to a 2011 study and a practice bulletin issued by the American College of Obstetricians and Gynecologists (ACOG), you state that medical abortion[12] regimens demonstrate an increase in complications and failures, including serious risks of hemorrhage, infection, and ongoing pregnancy, after 49 days gestation (Petition at 3-4).

Our review of the S-020 efficacy supplement in 2016 concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.[13] Complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of Mifeprex (with an indication for medical termination of intrauterine pregnancy through 49 days gestation) were 92.1 percent and 95.5 percent in the United States and French trials, respectively.[14] The studies reviewed in support of the 2016 approval for Mifeprex (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 Clinical Review of the S-020 efficacy supplement summarized clinical outcomes and adverse effects from 22 studies (7 in the United States and 15 from outside the United States) through 70 days gestation, using the currently approved regimen of 200 mg oral mifepristone with 800 mcg buccal misoprostol. The ranges of complete medical abortion rates calculated by the clinical reviewer were 93.2 percent to 98.7 percent in the United States studies, and 92 percent to 98 percent in the non-United States studies.[15]

Serious adverse events associated with the use of mifepristone through 70 days gestational age are rare. Per the current mifepristone labeling, the rates of serious adverse events are low: transfusions are 0-0.1 percent, sepsis is less than 0.01 percent, hospitalization related to medical abortion is 0-0.7 percent, and hemorrhage is 0.1 percent.[16] As discussed

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[12] In this response, the terms "medical abortion" and "medication abortion" both refer to the use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy.

[13] See 2016 Clinical Review available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf, at 32-38 and 47-47.

[14] See 1999 Medical Officer's Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf, at 11 (Table 1) and 16.

[15] See 2016 Clinical Review, supra n. 13, at 28-31.

[16] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

throughout this response, the benefit/risk assessment supported our 2016 conclusion that the product is safe and effective through 70 days gestation.

In support of your assertion that medical abortion demonstrates an increase in complications after 49 days gestation, you cite to Mentula, et al.,[17] a register-based, retrospective cohort study that included 18,248 women in Finland who underwent medical abortion between January 1, 2003, and December 31, 2006 (Petition at 3). As an initial matter, we note that the Mentula study was primarily designed to assess the immediate adverse events following medical abortion in the second trimester (13 to 24 gestational weeks as defined by the authors) and then compare those events to those identified with medical abortion in the first trimester (up to 12 gestational weeks as defined by the authors). The study was not designed to compare rates of complications across gestational weeks within the first trimester. It is true that the Mentula publication includes information on the percentages of women who had surgical evacuation following medical abortion and the percentages of women who had infection following medical abortion, based on weekly gestational age, from 5 weeks to 20 weeks gestation.[18] However, the data in the Mentula study are relatively old (2003-2006); in our 2016 review of the S-020 efficacy supplement, we conducted an extensive review of more recent data[19] and concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.

You also cite to ACOG Practice Bulletin No. 143, which states: "the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days."[20] This statement is based on a 1998 publication which evaluated patients undergoing medical abortion with mifepristone 600 mg and then oral misoprostol 400 mcg two days later.[21] The regimen studied in this 1998 publication is not the currently approved regimen for mifepristone in the United States. Further, ACOG Practice Bulletin No. 143 has been withdrawn and replaced by Practice Bulletin No. 225, which was published in October 2020 and no longer contains this statement.[22]

You also state that the failure rate of the approved regimen (which you refer to as the "buccal misoprostol regimen") increases as the gestational age increases, especially at

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[17] Mentula MJ, Niinimake M, Suhonen S, et al. Immediate Adverse Events After Second Trimester Medical Termination of Pregnancy: Results of a nationwide registry study, Human Reproduction. 2011;26(4):927-932.
[18] Id. at Fig. 2 and Fig. 3. Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of abortion completion rates accounts for the need for surgical intervention. In clinical studies we reviewed, success of medical abortion was defined as the complete expulsion of the products of conception without the need for surgical intervention.
[19] See 2016 Cross-Discipline Team Leader Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf, at 37 (Table 4).
[20] Petition at 3. See Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.
[21] Spitz I, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United Sates, NEJM. 1998;338 (18):1241-1247.
[22] See ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. Obstetrics and Gynecology 2020; 136(4); e31 to e47.

gestational ages greater than 49 days, relying on a 2015 meta-analysis,[23] and that the gestational limit should not have been increased (Petition at 3-4). We agree that the failure rate of medical abortion regimens, including the currently approved regimen, generally increases with increasing gestational age. However, the increase in failure rate with each incremental week of gestation, as described in approved mifepristone labeling and in this 2015 meta-analysis, is small, and we believe that the benefit/risk profile for medical termination of intrauterine pregnancy between 49 and 70 days gestation remains acceptable.

For these reasons, we deny your request that FDA limit mifepristone, in a regimen with misoprostol for the termination of intrauterine pregnancy, to 49 days gestation.

2. Dosage and Administration

a. Prescriber Qualifications

You state that FDA should limit the "ability" to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than permitting non-physicians to apply to be certified prescribers, because of the regimen's serious risks and because physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age (Petition at 4). We do not agree.

Healthcare providers who are licensed to prescribe can become certified in REMS programs if they are able to meet the applicable REMS requirements. To become certified to prescribe mifepristone under the Mifepristone REMS Program, the prescriber must review the prescribing information for mifepristone and complete a Prescriber Agreement Form. By signing the form, the prescriber agrees that they meet certain qualifications, including the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also: (1) be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care; or (2) be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.[24]

In our review of the S-020 efficacy supplement in 2016, we determined that available data support that Mifeprex is safe and effective when prescribed by midlevel providers, such as physician assistants and nurse practitioners, as well as by physicians.[25] Our 2016 review included four studies that evaluated the safety and efficacy of medical abortion when performed by non-physician healthcare providers. Two trials evaluated the currently

[23] Petition at 4, fn. 6 (citing Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21).
[24] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf; see also https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[25] See 2016 Clinical Review, supra n. 13, at 79; see also 2016 Cross-Discipline Team Leader Review, supra n. 19, at 17-18. We also note that in most states, midlevel clinicians, such as physician assistants and nurse practitioners, are licensed to prescribe medications.

approved Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner);[26,27] one trial studied a regimen using vaginal misoprostol (Warringer);[28] a fourth study did not specify the route of misoprostol administered (Puri).[29] Olavarrieta reported a completion rate of 97.9 percent when medical abortion was provided by nurses as compared with 98.4 percent with physicians. Kopp Kallner reported a completion rate of 99 percent with certified nurse midwives versus 97.4 percent with physicians. Warriner reported an abortion completion rate of 97.4 percent with nurses as compared with 96.3 percent with physicians. Puri reported an abortion completion rate of 96.8 percent when the service was provided by nurse-midwives as compared with 97.4 percent in the "standard care" group.[30] Our 2016 review also included a systematic review of six controlled clinical studies by Renner;[31] the authors concluded that the evidence "indicates that trained mid-level providers may effectively and safely provide first trimester surgical and medical termination of pregnancy services." Additionally, Barnard et al., in a Cochrane systematic review, assessed the safety and effectiveness of abortion procedures administered by mid-level providers (nurse practitioners, midwives, other non-physician healthcare providers) compared to doctors.[32] The authors concluded, based in part on two of the studies that we had reviewed in 2016,[33] that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors.

We also believe that the identification of patients for whom the use of mifepristone is contraindicated can be done by mid-level healthcare providers, as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:[34]

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass

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[26] Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus Physician-provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial. Bull World Health Organ. 2015;93:249-258.

[27] Kopp Kallner H, Gomperts R, Salomonsson E, et al. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. BJOG. 2015; 122: 510-517.

[28] Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet. 2011; 377: 1155-61.

[29] Puri M, Tamang A, Shrestha P, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. Reproductive Health Matters. 2015; 22(44) 94-103.

[30] 2016 Clinical Review, supra n. 13, at 43.

[31] Renner RM, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. BJOG 2013 Jan;120(1):23-31.

[32] Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). Cochran Database of Systematic Reviews. 2015, Issue 7.

[33] Of the medical abortion studies reviewed by Barnard et al (Id.), two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al (supra n. 28) and Kopp Kallner et al (supra n. 27). The third used a different dose of misoprostol than the currently approved regimen. See Jejeebhoy SJ, Kalyanwalaa S, Zaviera AJF, Kumara R, Mundleb S, Tankc J, et al. Feasibility of expanding the medication abortion provider based in India to include avurvedic physicians and nurses. International Perspectives on Sexual and Reproductive Health 2012;38(3)133-42)

[34] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

- An intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandins
- Hemorrhagic disorder or concurrent anticoagulant therapy
- Inherited porphyrias

These contraindications can be assessed by trained healthcare providers who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. We continue to believe that available data support the conclusion that mid-level healthcare providers, as well as physicians, possess the clinical and counseling skills necessary to provide medical abortion. We note this is consistent with ACOG's statement in its current practice bulletin that "[i]n addition to physicians, advanced practice clinicians, such as nurse-midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion."[35] Further, if necessary, ultrasound training and certification is available to nurse practitioners and physician assistants, as well as physicians.[36] In sum, available information supports that mid-level healthcare providers as well as physicians can determine whether mifepristone is an appropriate treatment for a particular patient and dispense it.

You also assert that FDA should strengthen the requirement that providers accurately assess the duration of the pregnancy by mandating that gestational age be assessed by ultrasound (Petition at 5). We refer you to FDA's 2016 Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (the "2016 CP Response"), where FDA stated that the determination of gestational age does not always require an ultrasound. In the 2016 CP Response, FDA stated it had "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS [transvaginal ultrasound]) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider."[37]

In the Petition, you reference the Prescriber Agreement Form, in which the provider must attest they have the ability to: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed (or have made plans to provide such care through others), and you state that a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional

[35] ACOG Practice Bulletin No. 225, supra n. 22.
[36] American Institute of Ultrasound in Medicine. Accessed November 26, 2021. https://www.aium.org/officialStatements/70.
[37] FDA's citizen petition response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical and Dental Association, and Concerned Women for America on August 20, 2002, Docket No. FDA-2002-P-0364 at 18. See https://www.regulations.gov/document/FDA-2002-P-0364-0002.

contraindications (Petition at 5-6). You state that FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4).

Certified prescribers do not have to be physically present with the patient as long as they have confirmed the patient's gestational age and intrauterine pregnancy. As noted above, in the 2016 CP response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."[38] Moreover, the evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber and can be done in different types of healthcare settings. A certified prescriber can also review the Patient Agreement Form[39] with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity. See also section II.B.1.c (ETASU C – In-person Dispensing).

With respect to providing surgical intervention in cases of incomplete abortion or severe bleeding and assuring patient access to medical facilities equipped to provide blood transfusions and resuscitation (if necessary), the Prescriber Agreement Form does not reflect a requirement that the certified prescriber must provide such care personally; rather, the prescriber must agree that they have the ability to provide such care or that they have made plans to provide such care through others, and that they have the ability to assure the patient has access to appropriate medical facilities. It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients, and in many places, hospitals employ "hospitalists" to provide care to all hospitalized patients. We also note ACOG's statement that "[i]n rare cases, a patient who undergoes a medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral."[40]

For these reasons, we deny your request that FDA limit the "ability" to prescribe and dispense mifepristone to licensed physicians, and we deny your request that FDA require certified providers to physically meet with and examine the patient.

b. Office Visits and Administration of Mifepristone/Misoprostol

In the Petition, you state that the use of mifepristone and misoprostol should require three office visits by the patient (Petition at 7). In support of this position, you state the following:

- Drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10).

[38] Id.
[39] See https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[40] ACOG Practice Bulletin Number 225 supra n. 22.

- Abortion complications are more frequent when women abort at home and more healthcare oversight is needed (Petition at 8).

- Home administration of misoprostol does not permit healthcare providers to control when their patients take misoprostol and without monitoring:

    - a patient may take buccal misoprostol before the minimum 24-hour period after taking Mifeprex, which leads to a significantly increased failure rate (Petition at 7).

    - a patient may swallow misoprostol rather than administer it buccally, and oral administration is not as effective as buccal administration in ending the pregnancy (Petition at 7).

- Because providers may now "confirm" that a patient's drug-induced abortion was successful without a clinic visit, this increases the threat that Rh-negative patients will not receive Rhogam, which is necessary to prevent serious risks in subsequent pregnancies (Petition at 7 and 9).

We address each of these points below.

i. Follow-up Care

The safe use of mifepristone when used in the approved regimen with misoprostol is not contingent on a specific number of office visits being made by the patient undergoing a medical termination of pregnancy. The 2016 labeling change for Mifeprex regarding post-treatment assessment, including the change to the approved regimen to reduce the number of offices visits from three to one, was based on evidence reviewed in the S-020 efficacy supplement. We concluded, upon reviewing the data, that three office visits were not necessary to assure the safe use of Mifeprex.[41]

In your Petition, you point to statements by ACOG that medical abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 8, 10). The ACOG statements you point to are from ACOG Practice Bulletin No. 143, which has been withdrawn and replaced by Practice Bulletin No. 225.[42] Neither of the statements from the withdrawn Practice Bulletin nor Practice Bulletin No. 225 contraindicate medical abortion in women who are not available for an in-clinic follow-up visit. The current ACOG recommendations indicate that for medical abortion, "[f]ollow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[43] The patient and their healthcare provider should determine the best option for follow-up as part of the consultation and consent process.[44] As reflected in ACOG's guidance, appropriate follow-

[41] See 2016 Clinical Review, supra n. 13, at 44 and 64-67.
[42] ACOG Practice Bulletin Number 225, supra n. 22.
[43] Id.
[44] Id.

up after medical termination of a pregnancy may be accomplished in multiple ways and not all require an in-clinic visit.

You also question findings in multiple studies that evaluated the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, or MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies and assessed the ability of patients to self-administer these tests and interpret the test results (Petition at 9-10). Overall, these studies concluded that in the majority of women, it is feasible to use a simplified test to determine if further follow-up is necessary. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion completed at home versus routine clinic follow-up after medical abortion, concluding self-assessment was not inferior to routine clinic follow-up.[45] We note that this is consistent with current ACOG recommendations, which state that "follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[46]

You also assert that it is important for a patient to be under observation after taking misoprostol to ensure that they are appropriately monitored and provided sufficient pain medication (Petition at 8). You cite the World Health Organization (WHO)'s statement in guidance that up to 90 percent of women will abort within 4-6 hours after taking misoprostol; you further state that the 2000 regimen permitted patients to be in the clinic during this time period (Petition at 8). Your reference to the WHO guidance document[47] appears to be out of context. The WHO guidance takes no position on whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol; in fact, it explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.[48] In the United States, and as reflected in the approved labeling, medical termination of pregnancy usually involves patients terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

ii. At Home Medical Abortion and Healthcare Oversight

In addition, you cite a 2018 study to support your statement that abortion complications are more frequent when women abort at home (Petition at 8). The study evaluated complications following medical abortion (both less than 12 weeks and more than 12 weeks gestation) as well as following surgical abortion, at one hospital in Sweden between 2008 and 2015.[49] For the years 2008 to 2010, data were collected retrospectively; for the years

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[45] Baiju, N, Acharya, G, D'Antonio, F, et al. 2019. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. BJOG; 126:1536-1544.

[46] ACOG Practice Bulletin Number 225, supra n. 22.

[47] World Health Organization, Safe Abortion: technical and policy guidance for health systems – 2nd edition. 2012. Page 45 and Section 2.2.2.1 Medication for pain.

[48] Id. at Section 2.3 Post-abortion care and follow-up, at 52.

[49] Carlsson I, Breding K, Larsson PG, 2018, Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study, BMC Women's Health 18:158.

2011 to 2015, data were collected prospectively. In this study, medical abortions after 12 gestational weeks all occurred at the hospital. The authors report that, among medical abortions less than 12 weeks, the complication frequency increased from 5.4 percent (2008 to 2010) to 8.2 percent (2015). However, the authors also compared the complications related to medical abortions that occurred at less than 12 gestational weeks between "at home" abortions (managed as an outpatient) and "at the hospital" abortions, in 2015 and found no statistically significant difference (8.2 percent "at home" versus 8.0 percent at the hospital). For pregnancies less than or equal to 9 gestational weeks, the rates are similar for the "at home" group (10.0 percent) and the "at the hospital" group (9.3 percent). Notably, as part of our review and approval of the S-020 efficacy supplement in 2016, we assessed serious adverse events by gestational age, including hospitalizations, serious infection requiring hospitalization or intravenous antibiotics, bleeding requiring transfusion, and ectopic pregnancy, as reported in the literature submitted by the Applicant. We concluded that these serious adverse events are rarely reported in the literature and that the regimen of mifepristone 200 mg followed by buccal misoprostol 800 mcg in 24-48 hours is safe to approve for use through 70 days gestation.[50]

You also state that medical abortion is a longer process than surgical abortion and that it requires more attention and care from healthcare providers (Petition at 10). We agree that medical abortion can be a longer process than surgical abortion,[51] but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. Not all of the complications associated with medical abortion necessarily require more intensive management from healthcare providers during a follow-up visit. The question of whether to include an in-person follow-up visit should be discussed by the healthcare provider and the patient. We have concluded that medical abortions are safe and effective for patients who are appropriate candidates and reducing the number of clinic visits does not compromise patient safety.

The current approved labeling for mifepristone for medical termination of pregnancy states that complete pregnancy termination "can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan." Not all these modalities require an in-clinic assessment during a follow-up visit. Our review of the S-020 efficacy supplement concluded that "available data support … that there are a variety of follow-up modalities that can adequately identify the need for additional intervention."[52] We note that these findings are also consistent with ACOG guidelines, which state that "[r]outine in-person follow-up is not necessary after uncomplicated medication abortion" and recommend several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at one week after treatment followed by urine pregnancy testing at four weeks after treatment.[53] Because there is more than one effective method to detect an on-going pregnancy, we conclude that the way in which post-treatment follow-up is performed may be determined by the healthcare provider and the patient.

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[50] 2016 Clinical Review, supra n. 13, at 51-57.
[51] See ACOG Practice Bulletin Number 225, supra note 22.
[52] 2016 Cross Discipline Team Leader Review, supra n. 19, at 17.
[53] ACOG Practice Bulletin Number 225, supra note 22.

iii. Misoprostol

In the Petition, you make a number of assertions regarding the use of misoprostol. We address each in turn.

First, you assert that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex, thereby rendering the regimen ineffective, and that home administration of misoprostol does not permit health providers to control when their patients take misoprostol (Petition at 7). You similarly assert that the use of buccal misoprostol sooner than 24 hours after administering mifepristone leads to significantly increased failure rates (Petition at 7).

As an initial matter, our review of the S-020 efficacy supplement in 2016 included data that evaluated the home use of misoprostol in over 30,000 women. The data showed that Mifeprex was safe and effective in a regimen with misoprostol when misoprostol was self-administered at home.[54] Therefore, any incorrect administration resulting in a failed abortion was infrequent and did not significantly affect the safety and efficacy of medical abortion. Furthermore, because the process of expelling the pregnancy may begin as soon as 2 hours after taking misoprostol, there is a benefit in allowing patients to choose when and where to start this process, to maximize the possibility of their being at a safe place at a convenient time to experience cramping and bleeding.[55]

In support of your assertion of significantly increased failure rates, you cite a pilot study by Lohr et al.[56] Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (less than or equal to 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations[57] using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates reported by Lohr at 24 hours for oral mifepristone and buccal misoprostol were 72.5 percent, 69.2 percent, and 72.5 percent, respectively; the complete abortion rates at two weeks, however, were 97.5 percent, 100 percent, and 94.9 percent, respectively (and are consistent with the completion rates as described in the approved labeling).[58] The published complete abortion rates at 24 hours for simultaneous oral mifepristone and vaginal misoprostol administration were 90 percent, 88 percent, and 83 percent, respectively, for the gestational age groupings and the complete abortion rates at 2 weeks were 98 percent, 93 percent, 90 percent, respectively. Based on the data presented in Lohr,

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[54] See 2016 Clinical Review, supra n. 13, at 41 and 48.
[55] Id. at 38.
[56] Petition at 7 (referencing Lohr PA, Reeves MF, Hayes JL, et al., 2007, Oral Mifepristone and Buccal Misoprostol Administered Simultaneously for Abortion: A Pilot Study, Contraception, 76:215-220).
[57] Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. Contraception 2005;71:447–50; Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. Contraception 2005;71:333–6.
[58] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. As recommended in Section 2.3 of the approved labeling, follow-up at 7-14 days after administration of mifepristone is more appropriate to evaluate efficacy.[59] It is misleading to only reference the abortion completion rates observed at the 24-hour timepoint from Lohr. Therefore, we do not agree that data from Lohr indicate higher failure rate with misoprostol taken before the prescribed minimum 24-hour period after taking mifepristone.

Although we disagree that Lohr demonstrates a higher failure rate with misoprostol taken before 24-hours after taking mifepristone, we note that our 2016 review of the S-020 efficacy supplement referenced a 2013 systematic review by Raymond, which concluded that if the interval between mifepristone and misoprostol interval is less than or equal to 24 hours, the procedure is less effective compared to an interval of 24-48 hours.[60] As explained above, the data reviewed in 2016 showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective. Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. However, in light of the data reviewed, section 2.1 of the labeling approved in 2016 (as well as the currently approved labeling and Medication Guide) states that there should be a "minimum 24-hour interval between" mifepristone and misoprostol (emphasis included in the labeling).[61] The approved dosing regimen also states that misoprostol is taken within 24 to 48 hours after taking mifepristone and acknowledges that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration.

In addition to your concerns that a woman may take misoprostol too soon after administering mifepristone, you also state that waiting until 24 hours after administering mifepristone does not guarantee success (Petition at 7-8). In support of this concern, you cite a 2015 review by Chen and Creinin. You state that this review found "women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen" (Petition at 8). Chen and Creinin included studies in which the intervals between mifepristone and buccal misoprostol were 24 hours or 24-48 hours and stated that "based on the available literature, the overall efficacy of regimens with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2 percent compared with 96.8 percent)."[62] The rate differences were statistically significant, but both regimens were more effective than the 92 percent efficacy rate of the original regimen approved in 2000 (administering misoprostol 48 hours after taking mifepristone).

Finally, you also express concern that if misoprostol is self-administered, a woman may swallow it rather than keep the pill between her cheek and gum, and oral administration of

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[59] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

[60] 2016 Clinical Review, supra n. 13, at 31 (citing 8 Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.)

[61] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

[62] See Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. Obstet Gynecol. 2015;126(1):12-21; see also 2016 Clinical Review, supra n. 13, at 21.

misoprostol (i.e., swallowing the pill) following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy (Petition at 7). Winikoff et al. specifically studied the use of oral compared to buccal misoprostol 24-36 hours after mifepristone 200 mg with overall success rates of 91.3 percent and 96.2 percent, respectively.[63] Both regimens resulted in a greater than 91 percent successful medical abortion. Although the study showed decreased efficacy with oral versus buccal administration in 57-63 days gestational age, there were no statistical differences in other gestational age groupings. Even assuming there is a small proportion of women who are 57-63 days gestational age and use oral administration of misoprostol (rather than buccal as labeled), a small decrease in the reported efficacy in that population would not justify requiring a clinic visit for all women undergoing medical abortion.

Overall, studies support the efficacy of the mifepristone, in a regimen with misoprostol when taken by the patient at home, Therefore, we do not agree that an in-person visit is necessary to manage administration of misoprostol.

iii. Rh-Negative Patients

In the Petition, you state that a follow-up examination is particularly critical for Rh-negative patients and that without that follow-up examination, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9). You suggest that a clinic visit after the administration of Mifeprex is important for Rh-negative women to receive Rhogam and that removing the required follow-up visit puts Rh-negative women at risk for isoimmunization. We do not agree.

Rh testing is standard of care in the United States and RhD immunoglobulin (such as Rhogam) should be administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).[64] However, the facility where the RhD immunoglobulin injection occurs (clinic, hospital or laboratory) is not critical. A shift from medical clinics to hospitals for administration of injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.[65] This has resulted in pregnant women frequently obtaining routine 28-week RhD immunoglobulin injections at hospitals/laboratories with a prescription provided by their healthcare providers. This same process of obtaining RhD immunoglobulin via prescription is available to patients after medical termination of pregnancy and does not require a follow-up clinic visit.

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[63] Winikoff B, Dzuba, IG, Creinin MD, et al, 2008, Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion, Obstet Gynecol 112(6):1303-1310.
[64] ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.
[65] See https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers.

In summary, the totality of data on the efficacy and safety of medical abortion at less than 70 days gestation, derived from numerous studies, has characterized the complications and rates of complications for completing medical abortion at home, and the findings show medical abortion at home is both safe and effective without three office visits. We therefore deny your request that the use of mifepristone in a regimen with misoprostol require three office visits by the patient.

c. Contraindications

In the Petition, you assert that critical language contraindicating Mifeprex for patients without access to appropriate emergency medical care was excluded from the 2016 Mifeprex labeling. You cite to a study[66] and ACOG statements as evidence that medical abortions have greater risks and more need for emergency "operation" than a surgical abortion, particularly for patients in rural areas with limited access to emergency medical care (Petition at 11).

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in section 4 of the approved labeling when we approved the S-020 efficacy supplement, the 2016 Mifeprex labeling and the currently approved mifepristone labeling, as well as the Mifepristone REMS Program, continue to include appropriate instructions for providers regarding patient access to appropriate medical care.[67] For example, the Boxed Warning includes language directing healthcare providers to ensure that the patient knows whom to call and what to do, including potentially going to an emergency room, if the patient experiences serious events associated with the use of mifepristone. The labeling also directs healthcare providers, as part of the dosing regimen, to give the patient the name and phone number of a healthcare provider who will be handling emergencies.[68] In addition, one of the required qualifications listed in the Prescriber Agreement Form is the "[a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."[69] Therefore, although certain language about access to medical facilities was removed from the approved labeling in 2016, we disagree that critical language about access to appropriate emergency medical care is lacking from the approved labeling.

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[66] See Petition Reference Document No. 17 (Harrison Affidavit: Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015), ¶115 (referencing M. Niinimaki et al., Immediate Complications after Medical compared with Surgical Termination of Pregnancy, Obstet. Gynecol. 114:795 (Oct. 2009)).

[67] See Mifeprex labeling, approved 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf. See also current labeling at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

[68] Id.

[69] Mifepristone REMS Program, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390. Emphasis added.

You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.[70] As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

d. Adverse Event Reporting

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

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[70] Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.

You state that FDA should provide guidance to emergency healthcare providers and physicians so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13). We disagree that specific guidance is needed at this time. In the past, when appropriate, FDA has worked with the NDA Applicant to issue communications to healthcare providers and emergency department providers concerning certain serious adverse events.[71] Furthermore, the approved Medication Guide advises patients to take the Medication Guide with them if they need to go to the emergency room or seek care from a healthcare provider other than the one who dispensed the medication to them, so the emergency room or healthcare provider understands the patient is having a medical abortion. We have not identified a change in the safety profile of mifepristone that would warrant additional communications to healthcare providers and emergency department providers concerning complications following medical abortion. If we become aware of safety information that merits further communications with emergency department providers or healthcare providers, or that warrants revisions to the approved labeling, we will act as appropriate.

You also assert that many Mifeprex prescribers "violate FDA protocol," instructing their patients to lie to emergency medical personnel, and that this prevents emergency healthcare providers from appropriately caring for their patients and further decreases the likelihood that adverse events will be reported (Petition at 12). Your only support for this claim is a reference to instructions from the organization Aid Access[72] to patients that they can tell emergency room staff that they had a miscarriage and do not need to tell medical staff that they had a medical abortion. The Petition does not provide any data or additional information establishing "many Mifeprex prescribers violate FDA protocol, instructing their patients to lie," or that these providers thereby prevented appropriate care and decreased the number of adverse events reported.

B. REMS

1. Request to Retain Mifeprex REMS

In your Petition, you request that FDA retain the Mifeprex REMS (Petition at 14). We agree that a REMS is necessary to ensure that the benefits of mifepristone in a regimen with misoprostol outweigh the risks. FDA's determination as to whether a REMS is necessary

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[71] See Historical Information on Mifepristone (Marketed as Mifeprex), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm. For example, the NDA applicant and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 and a Dear Emergency Room Director letter in September 2004. The fact that these letters were issued does not imply that the approved mifepristone regimen is unsafe; it is not uncommon for drug sponsors to issue "Dear Health Care Provider" letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, "[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely."

[72] We note that Aid Access facilitated the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA sent Aid Access a warning letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers. US FDA Warning Letter to Aidaccess.org, dated March 8, 2019. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019.

to ensure that the benefits of a drug outweigh its risks is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case.[73] In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.[74]

As described in the background section of this response (see section I.A.), FDA determined that interventions in addition to the FDA-approved labeling were necessary to ensure that the benefits of Mifeprex outweighed its risks when the drug was initially approved in 2000, and periodic re-evaluations of the REMS since that time have reached the same conclusion. As further described in the background section of this response (see section I.E.), FDA recently undertook a review of the Mifepristone REMS Program. As explained below, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risks.

After review of multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FAERS reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation,[75] as well as information submitted by the Applicants, we have concluded that the REMS can be modified to reduce the burden on the health care delivery system without compromising patient safety. As explained below, we agree that the healthcare provider certification (ETASU A) and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions (ETASU D) continue to be necessary components of the REMS to ensure the benefits outweigh the risks. However, we have concluded that the Mifepristone REMS Program must be modified to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

Below, we discuss each of these elements of the Mifepristone REMS Program.

a. ETASU A – Prescriber Certification/Qualifications

ETASU A under the Mifepristone REMS Program requires healthcare providers who prescribe mifepristone to be certified. In order to become certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the Prescriber Agreement Form. In signing the Prescriber Agreement Form, prescribers agree they meet the qualifications listed below:

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[73] See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Apr. 2019).
[74] Id.
[75] See supra n. 10.

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- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the Patient Agreement Form with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

Our review of the published literature did not identify any studies comparing healthcare providers who met these qualifications with healthcare providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention either personally or through others, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our conclusion continues to be that a healthcare provider who prescribes mifepristone in a regimen with misoprostol should meet the above qualifications. Absent these provider qualifications, we are concerned that serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, may not be detected or appropriately managed.

Accordingly, we have determined that ETASU A must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks. Maintaining the requirement for prescriber certification ensures that providers meet the necessary qualifications and adhere to the guidelines for use listed above. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one-time for each applicant.

Although we agree with your request to retain the REMS for mifepristone (now the Mifepristone REMS Program) insofar as it pertains to ETASU A, as discussed in section II.A.2.a of this response, we do not agree with your request that the healthcare provider needs to be a licensed physician to meet this requirement.

b. ETASU D – Requirement For The Drug To Be Dispensed With Evidence Or Other Documentation Of Safe-Use Conditions

ETASU D under the Mifepristone REMS Program requires mifepristone to be dispensed with evidence or other documentation of safe-use conditions. To receive mifepristone for medical termination of intrauterine pregnancy through 70 days gestation, the patient must sign a Patient Agreement Form indicating that the patient has received, read, and been provided a copy of the Patient Agreement Form and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The Patient Agreement Form ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication. In a number of approved REMS, Patient Agreement Forms or Patient Enrollment Forms ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[76]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the Patient Agreement Form with the patient, fully explaining the risks of the treatment regimen and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the Patient Agreement Form, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the Patient Agreement Form serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed Patient Agreement Form in the patient's medical record.

In addition, we conducted an updated review of published literature since 2016 to assess the utility of maintaining the Patient Agreement Form as part of the Mifepristone REMS Program, and these studies do not provide evidence that would support removing ETASU D. For these reasons, we have determined that ETASU D must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks.

[76] REMS@FDA, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.

c. ETASU C – In-Person Dispensing

ETASU C under the Mifepristone REMS Program currently requires mifepristone to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. This creates what we refer to in this response as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office, or hospital when the drug is dispensed. The mifepristone REMS document currently states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than a clinic, medical office, or hospital. As explained below, based on a recent review of the REMS, we believe that the Mifepristone REMS Program must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks. This conclusion is based on our review of information from the Mifepristone REMS Program one-year (1st) REMS[77] assessment data and postmarketing safety information, and supported by our review of the published literature.

i. Assessment Data

As part of our review of the REMS, we evaluated information included in the 1st REMS assessment report for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, and non-compliance data. This 1st REMS assessment report covers a reporting period between April 11, 2019 through February 29, 2020. During this reporting period, a small number of non-compliance events were reported.

As described in section I.C. of this response, during the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not enforced. To better understand whether there was any impact on safety or non-compliance during the periods when the in-person dispensing requirement was not enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or non-compliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. The NDA and the ANDA Applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no

[77] This REMS assessment report was the first submitted following the approval of the single, shared system REMS for mifepristone.

indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events.

ii. FAERS/Postmarketing Safety Data

FDA routinely monitors postmarketing safety data for approved drugs through adverse events reported to our FAERS database,[78] through our review of published medical literature, and when appropriate, by requesting applicants submit summarized postmarketing data. For our recent review of the REMS, we searched our FAERS database, reviewed the published medical literature for postmarketing adverse event reports for mifepristone for medical termination of pregnancy, and requested that the Applicants submit a summary and analysis of certain adverse events. Our review of this postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced.

In order to evaluate the periods when in-person dispensing was and was not enforced, we conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy. The data for this time period were then further divided into the date ranges when in-person dispensing was enforced per the REMS (January 27, 2020 - July 12, 2020 and January 13, 2021 - April 12, 2021) versus when in-person dispensing was not enforced: July 13, 2020 - January 12, 2021 (in-person dispensing enforcement was temporarily enjoined) and April 13, 2021 - September 30, 2021 (enforcement discretion for in-person dispensing because of the COVID-19 PHE).

Based on the above search, a total of eight cases were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when in-person dispensing was being enforced (i.e., January 27, 2020-July 12, 2020 and January 13, 2021-April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when in-person dispensing was not enforced (i.e., July 13, 2020-January 12, 2021 and April 13, 2021-September 30, 2021); however, the narratives provided in the FAERS reports for three of the five cases explicitly stated that mifepristone was dispensed in-person. These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Of note, ongoing pregnancy and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case reported the occurrence of oral pain/soreness (case 8) in July

[78] FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

2021, but did not provide sufficient information to determine the exact date of the adverse event.

As discussed in section II.A.2.d., the Applicants report adverse events, including serious adverse events, to FDA in accordance with applicable regulations.[79] To enable additional review of adverse events, Applicants were requested to provide a summary and analysis for adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided the requested summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021. The Applicant for the generic provided the requested summary of postmarketing safety information from April 11, 2019 (date of initial approval) through September 30, 2021. The information provided by the Applicants included the same cases identified in FAERS, as discussed above.

We analyzed the FAERS data referenced above to determine if there was a difference in adverse events when in-person dispensing was and was not enforced. Based on FDA's review of this data, we concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced and that mifepristone may be safely used without in-person dispensing. FDA's review of the summary and analysis data submitted by the Applicants (which, as noted above, included the same cases identified from FAERS) did not change this conclusion.

iii. Published Literature

As noted above, we also conducted an extensive review of the published literature since March 29, 2016 (the date the S-020 efficacy supplement for Mifeprex was approved) through September 30, 2021.[80] Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or equivalent healthcare provider in countries other than the United States). Some studies have examined replacing in-person dispensing in certain healthcare settings with dispensing at retail pharmacies[81]

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[79] See 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81.

[80] In support of your request that we retain the REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber, you reference two studies that you assert do not comply with the REMS (Petition at 19-22). Outcomes from both of the studies you reference have been reported in the published literature and are addressed in the discussion that follows. We note that as a general matter, a clinical investigation of an approved drug that is subject to a REMS can take place in healthcare settings outside those provided for in the REMS. When an approved drug that is subject to a REMS is studied in a clinical trial, the REMS does not apply to the use of the drug in that clinical trial. However, FDA reviews the protocol to ensure that it will be conducted in a manner that adequately addresses the risks that the REMS is intended to mitigate, such that the trial participants will not be exposed to an unreasonable and significant risk of illness or injury. See 21 CFR 312.42(b)(1)(i) and (b)(2)(i).

[81] Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. Obstet Gynecol 2021;137:613–22; Rocca CH, Puri M, et al. Effectiveness and safety of early medication

and dispensing mifepristone from pharmacies by mail.[82] Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to patients,[83] and (2) prescribers using couriered delivery of medications.[84] Different studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization."[85]

We note that the ability to generalize the results of these studies to the United States population is hampered by differences between the studies with regard to pre-abortion care (e.g., telemedicine versus in-person). In addition, the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy. There are also factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation (for example, most studies on mail dispensing of mifepristone also include telemedicine consultation); and (2) because most serious adverse events with medical abortion are infrequent, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States. Despite the limitations of the studies we reviewed, we have concluded that overall the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

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abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. PLoS ONE 13(1): e0191174. https://doi.org/10.1371/journal.pone.019117; Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. Contracept X. 2020; 2: 100023.

[82] Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2021, ISSN 0010-7824, https://doi.org/10.1016/j.contraception.2021.09.008, Available online 20 September 2021; Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. JAMA Network Open. 2021;4(8):e2122320, doi:10.1001/jamanetworkopen.2021.22320; Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. Aust N Z J Obstet Gynaecol 2018;58: 335-340.

[83] See Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. Contraception 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online. Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. Contraception 2019; 100:173-177. See also Chong et al., infra n. 103 Kerestes et al., infra n. 105, and Aiken et al., infra n. 106.

[84] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.

[85] Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. BJOG 2019;126;609-618. Norten H, Ilozumba O, Wilkinson J, Gemzell Danielsson K, Gomperts R. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. BJOG 2021; https://doi.org/10.1111/1471-0528.16765; Aiken ARA, Digol I, Trussell J, Gomperts R. Self-reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. BMJ 2017;357:j2011 http://dx.doi.org/10.1136/bmj.j2011.

Below is a summary of our review of the literature, organized by the methods of dispensing mifepristone that were studied.

(a) Retail pharmacy dispensing

Three studies reported medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation (Grossman,[86] Rocca,[87] Wiebe[88]). Grossman conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic. Complete abortion without additional procedures occurred in 93.5 percent of participants with known outcomes. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. No participants experienced a serious adverse event, were hospitalized or required transfusion. Three participants had emergency department (ED) visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study safety and efficacy outcomes are consistent with labeled outcome frequencies. The study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to United States retail pharmacies; there is insufficient information to assess this.

Rocca[89] conducted an observational study evaluating participants who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. The authors reported that, with respect to complete abortion (greater than 97 percent) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[90] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of women who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (equal to or greater than 95 percent participants with known outcomes). The telemedicine group had one case of hemorrhage (0.5 percent) and one case of infection requiring antibiotics (0.5 percent) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3 percent compared to 1.5 percent in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

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[86] Grossman et al., supra n. 81.
[87] Rocca et al., supra n. 81.
[88] Wiebe et al., supra n. 81.
[89] Rocca et al., supra n. 81.
[90] Wiebe et al., supra n. 81.

None of the three studies allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the results of the studies to the current retail pharmacy environment in the United States. The outcome findings from the one United States study (Grossman)[91], in which the pharmacies were partnered with prescribers, are unlikely to be broadly generalizable to the current retail pharmacy environment and do not reflect typical prescription medication availability with use of retail pharmacy dispensing. For the retail pharmacy dispensing study in Canada (Wiebe),[92] timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that would allow timely access to medications for medical abortion would occur in retail pharmacies throughout the United States, suggesting the findings from that study may not be broadly generalizable. The third study (Rocca)[93] evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the United States retail setting.

(b) Mail order pharmacy

Three studies evaluated mail order pharmacy dispensing (Grossman,[94] Upadhyay,[95] Hyland[96]). Grossman published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. Complete abortion without additional procedures occurred in 96.9 percent of participants with known outcomes. Two (0.9 percent) participants experienced serious adverse events; one received a blood transfusion and one was hospitalized overnight. Nine (4 percent) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies.

Upadhyay[97] reports findings from a retrospective cohort study of women undergoing medical abortion in the United States without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Abortion outcome was determined by either an assessment on day 3 or a 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95 percent for participants with known outcomes and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. As recommended in Section 2.3 of the approved labeling, follow-up at

[91] Grossman et al., supra n. 81.
[92] Wiebe et al., supra n. 81.
[93] Rocca et al., supra n. 81.
[94] Grossman et al, supra n. 82.
[95] Upadhyay et al., supra n. 82.
[96] Hyland et al., supra n. 82.
[97] Upadhyay et al., supra n. 82.

7-14 days after administration of mifepristone is more appropriate to evaluate safety and efficacy. This study used a model with numerous deviations from standard provision of medical abortion in the United States, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[98] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. Complete abortions without additional procedures occurred in 96 percent of participants with documented outcomes and is consistent with labeled efficacy. Of the participants included in the analysis, 95 percent had no face-to-face clinical encounters after medications were mailed while 3 percent were admitted to the hospital and 2 percent had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up." The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. However, the reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported frequency of hospitalizations (3 percent) is higher than the less than 1 percent in the FDA-approved mifepristone labeling, conclusions on the safety findings cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that efficacy of medical abortion is maintained with mail order pharmacy dispensing. With respect to safety, in the Grossman study[99] the interim analysis, although small, does not raise serious safety concerns. Safety findings from the Hyland[100] study are difficult to interpret. Although only one transfusion is reported and the authors state the findings demonstrate safety, a higher hospitalization rate and lack of information on the reasons for hospitalization preclude reaching any conclusions about the safety findings. Lastly, the Upadhyay[101] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the United States.

(c) Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail. Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population exclusively: Raymond (outcomes from May 2016 to December

[98] Hyland et al., supra n. 82.
[99] Grossman et al., supra n. 82.
[100] Upadhyay et al., supra n. 82.
[101] Hyland et al., supra n. 82.

2018),[102] Chong (outcomes from May 2016 to September 2020)[103] and Anger (outcomes from March 2020 to September 2020).[104] A fourth study, Kerestes,[105] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020 and a fifth study, Aiken (2021)[106] reports outcomes of medical abortion up to 70 days gestational age in the United Kingdom before and during the COVID-19 PHE in a retrospective cohort study.

In Raymond,[107] complete abortion without additional procedures occurred in 93 percent of participants with known outcomes. There were two hospitalizations (one participant received a transfusion for severe anemia despite having had a complete abortion) and 7 percent of participants had clinical encounters in ED/urgent care centers. The reported outcomes are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).[108] Of note, the authors state that half of the ED/urgent care visits did not entail any medical treatment. In Chong,[109] approximately 50 percent of the medical abortions occurred during the period of the COVID-19 PHE. Complete abortion without an additional procedure occurred in 95 percent of those with known outcomes. Transfusions were 0.4 percent and hospitalizations were 0.7 percent; 6 percent of participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 4.1 percent to complete abortion. The reported outcomes in Chong (which updated the findings described in Raymond) are similar to outcomes described in approved labeling except that (as with the Raymond study it updated) the combined ED/urgent care center encounters (6 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).

Anger,[110] which compared outcomes among participants enrolled in the Gynuity study who did ("test medical abortion cohort") versus did not ("no-test medical abortion cohort")[111]

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[102] Raymond et al., supra n. 83.
[103] Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. Contraception 2021;104:43-48.
[104] Anger et al., supra n. 83.
[105] Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021 Jul;104(1):49-53. doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.
[106] Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. BJOG 2021;128:1464–1474.
[107] Raymond, supra n. 83.
[108] The authors reported the combined frequency of emergency department/urgent care visits, whereas the approved labeling includes the frequency for emergency department (emergency room) visits. Therefore it is unknown whether the frequency of emergency department visits in the trial, as distinct from the combined frequency of emergency department/urgent care visits, is comparable to the frequency of emergency department visits reflected in approved labeling.
[109] Chong et al., supra n. 103.
[110] Anger et al., supra n. 83.
[111] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al." (Raymond EG, Grossman D, Mark A, et.al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. Contraception 2020;101:361-366)

have confirmation of gestational age/intrauterine location with an examination or ultrasound, found that those without an examination or ultrasound prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.[112] There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the "test" group, complete medical abortion was confirmed in 98 percent of participants with known outcomes; one participant was "hospitalized and/or blood transfusion" and 8 percent had an unplanned clinic encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion). In the "no-test" group, complete medical abortion was confirmed in 94 percent of participants with known outcomes; two participants were "hospitalized and/or blood transfusion" and 12.5 percent had an unplanned clinical encounter.

Kerestes[113] included three different delivery models: traditional in-person visits, telemedicine consultation with in-person pick-up of medications, and telemedicine consultation with delivery of medications by mail (most of the latter were enrolled through Gynuity's TelAbortion study). Among participants with follow-up data, the rates of successful medical abortion without surgery were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine plus in-person pickup group). Although ED visits occurred the most frequently in the telemedicine plus mail group (four participants or 5.8 percent) and the least in the in-person group (two participants or 2.1 percent), the study reported no increases in other serious adverse events. Aiken (2021)[114] reported outcomes before and during the pandemic in a retrospective cohort study in the United Kingdom. The study compared the two cohorts: one before the pandemic with in-person visits and dispensing (traditional model) and one during the pandemic with either an in-person visit and in-person dispensing or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Complete abortion occurred in greater than 98 percent in both cohorts; the rate was slightly higher in the telemedicine group than in the in-person group. There were no significant differences in the rates of reported serious adverse events. The investigators' analysis determined that the efficacy and safety were comparable between both cohorts and concluded the hybrid model for medical abortion is effective and safe.

Taken together, data from the three Gynuity study reports (Raymond, Chong, and Anger), Kerestes, and Aiken (2021) support that efficacy of medical abortion was maintained when mifepristone was dispensed by mail from the clinic. Study reports of Raymond, Chong, and Kerestes all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail from the clinic, but without increases in other serious adverse events. Anger's comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. The Aiken (2021) study appears to be of sufficient

[112] We note that the two cohorts were not randomized in the Anger study; they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.
[113] Kerestes et al., supra n. 105.
[114] Aiken et al., supra n. 106.

sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, significant limitations include that the analysis was based on deidentified information and the investigators were unable to verify the outcomes extracted. Further, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

Notwithstanding the limitations discussed above, these studies overall support that dispensing by mail from the clinic is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use.

(d) Clinic dispensing by courier

Reynolds-Wright[115] reported findings from a prospective cohort study of participants at less than 12 weeks gestational age in Scotland undergoing medical abortion at home that provided mifepristone for pick up at the service or by couriered delivery to woman's home. The outcomes from this study in Scotland are consistent with the outcomes in the approved mifepristone labeling. However, the number of couriered deliveries was not reported. Thus this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. The study shares the same limitations as the Aiken (2021) study; the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

(e) Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail. WoW uses a model with numerous deviations from the standard provision of medical abortion in the United States. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Three studies (Endler, Norten, and Aiken (2017))[116] reported outcomes based on dispensing through this model. Endler and Norten reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail because neither provide meaningful outcomes data for consideration. Although Aiken (2017) is a large cohort study, the outcomes are self-reported and an unusually high rate of outcomes are unaccounted for; these limitations result in the data being insufficient to determine the safety of dispensing mifepristone by mail though a partner organization.

In sum, there are insufficient data from the literature we have reviewed to determine the safety and efficacy of dispensing from a retail pharmacy, by courier, or by a partner organization. With respect to dispensing mifepristone by mail, our review of the literature indicates that dispensing mifepristone by mail from the clinic or from a mail order

[115] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.
[116] Endler et al., Norten et al., and Aiken et al., supra n. 85.

pharmacy does not appear to jeopardize the efficacy of mifepristone for medical abortion. While the studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, the safety and efficacy outcomes reported in these studies remain within the ranges labeled for the approved mifepristone products. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other significant adverse events related to mifepristone use.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, and our review of the literature, we conclude that mifepristone will remain safe and effective if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added. Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the Mifepristone REMS Program, the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

In your Petition, you state that "[e]liminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls" and that "health care providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs" (Petition at 18-19).

We do not agree that eliminating the REMS requirement for the dispensing of Mifeprex in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of healthcare providers to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. There are many factors that contribute to patient safety, including evaluation of a patient, informed consent, development of a follow-up plan, and provision of a contact for emergency care. All of these can occur in many types of healthcare settings. The evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber.

You also assert that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19). We do not agree. Healthcare providers who prescribe mifepristone are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the American Medical Association that a healthcare provider-patient relationship is entered when the "physician serves a patient's medical needs;"[117] in the context of medical abortion, this

[117] See www.ama-assn.org/delivering-care/ethics/patient-physician-relationships.

healthcare provider-patient relationship continues until resolution of the pregnancy or transfer of care to another healthcare provider.[118]

We also note that patients who are not pregnant at the time of evaluation would not be appropriate candidates for being prescribed mifepristone for medical termination of pregnancy because they do not fulfill the approved indication of having an intrauterine pregnancy of up to 70 days gestation.

2. Other Safety Issues and Additional Studies

In support of your request that we retain the Mifeprex REMS, you cite the Council for International Organizations of Medical Sciences' (CIOMS) definition of "rare" to assert that because "about 1 out of 100 women" using Mifeprex and misoprostol require surgery, serious complications are common, not rare (Petition at 15-16).[119] Although we agree that certain elements of the Mifepristone REMS Program are necessary to assure the safe use of mifepristone, we do not agree with your assertion.

In the Petition, you state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and you cite the Medication Guide as stating "'*rarely*, serious and potentially life-threatening bleeding, infections, and other problems can occur following . . . medical abortion.' Specifically, 'in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure." (Petition at 15). Using these two separate statements in the Medication Guide, you argue that the CIOMS's definition of rare ("1 out of 1000") means that if 1 out of 100 women using Mifeprex in a regimen with misoprostol require surgery, serious complications are common, not rare. (Petition at 16). However, your reference to the two sentences in the Medication Guide conflates two different clinical scenarios: (1) the adverse event of serious and potentially life-threatening bleeding, and (2) treatment failure.

The first sentence you reference states: "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." This statement refers to life-threatening adverse events that can occur during termination regardless of gestational age or during miscarriage or childbirth regardless of the mode of delivery (e.g., vaginal delivery or cesarean section). At the time of our review of the clinical studies submitted to support the S-020 efficacy supplement, the reported rate of death in the studies reviewed, based on one death, was 0.007 percent (very rare under the CIOMS definition).[120] The rate of infections requiring hospitalization or

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[118] See https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine.

[119] Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition. 1999. https://cioms.ch/wp-content/uploads/2018/03/Guidelines-for-Preparing-Core-Clinical-Safety-Info-Drugs-Report-of-CIOMS-Working-Group-III-and-V.pdf. Accessed December 13, 2021 (CIOMS).

[120] Id. at 36 (defining the "very rare" standard category of frequency as less than 0.01 percent).

intravenous antibiotics was less than 0.1 percent (rare under the CIOMS definition),[121] and rates of transfusion were 0.03-0.7 percent (rare to uncommon under the CIOMS definition).[122] Therefore, "rarely" accurately refers to the frequency of the adverse events referenced in this statement.

The second sentence you reference from the Medication Guide states: "In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C)." This statement refers to the rate of surgical procedures for bleeding following treatment with mifepristone. Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the CIOMS definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion. Furthermore, in the vast majority of medical abortions, surgical intervention is not necessary.

You also cite a 2009 study and a 2018 study to assert that medical abortions carry greater risks than surgical abortions (Petition at 16). The 2009 Niinimaki, et al.[123] study reported overall incidences of immediate adverse events (up to 42 days) in medical and surgical abortions performed in women undergoing induced abortion from 2000-2006 based on data from the Finnish national registries. We agree that the overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0 percent versus 5.6 percent). Specifically, the incidence of hemorrhage, incomplete abortion, and surgical (re)evacuation were higher for medical abortion. However, the authors specifically noted that because medical abortion is associated with longer uterine bleeding, the high rate of events, which were pulled from a national registry reflecting both inpatient and outpatient visits, is not surprising. They opined that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy; the incidence of such bleeding was relatively low, although it was more common with medical abortion. In addition, the authors acknowledged there are inherent weaknesses in registry-based studies; there is variable reliability both of diagnoses and of severity of diagnoses. Nevertheless, the authors concluded that both methods are generally safe and recommended discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination.

We note that Ireland, et al.[124] reported findings from a more recent retrospective cohort study of 30,146 United States women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6 percent and 99.8 percent for medical and surgical abortion, respectively.

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[121] Id. at 36 (defining the "rare" standard category of frequency as greater than or equal to 0.01 percent and less than 0.1 percent).
[122] Id. at 36 (defining the "uncommon" standard category of frequency as greater than or equal to 0.1 percent and less than 1 percent); see also 2016 Clinical Review, supra n. 13, at 47 and 51.
[123] Niinimaki M, Pouta A, Bloigu A, et al. Immediate complications after medical compared with surgical termination of pregnancy. Obstet Gynecol. 2009;114(4):795-804.
[124] Ireland LD, Gatter, M, Chen, A. 2015. Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the Frist Trimester. Obstetrics & Gynecology 126;22-28.

Unanticipated aspiration for persistent pain, bleeding or both were 1.8 percent and 0.4 percent for medical and surgical abortion respectively. These findings are compatible with the Niinimaki study findings. There was no difference in major adverse events as defined by the authors (emergency department visit, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion) between the groups. The authors conclude medical and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

The 2018 Carlsson study is addressed above in section II.A.2.b.ii. of this response; as discussed above, that study showed no statistically significant difference between the overall complication rates between an "at home" and "at the hospital" abortion.[125]

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical abortion. However, as noted above, in the vast majority of medical abortions, surgical intervention is not necessary. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. Patients and their healthcare providers should discuss which method is preferable and safer according to each woman's unique situation.

You state that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13-14). As we explain below, additional studies are not needed at this time.

In justifying your assertion that a formal study is required in patients under the age of 18, you state that Mifeprex was approved for use in the pediatric population in 2000 after the requirement for studies in the pediatric population was waived (Petition at 13-14). The approved indication for mifepristone does not limit its use by age. Although patients age 17 and under were not included in the clinical trials supporting the initial approval of Mifeprex in 2000, we stated at the time that the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents. Our conclusion in 2000 that pediatric studies of Mifeprex were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time. Because we determined that there were sufficient data from studies of mifepristone, the original Mifeprex approval should have reflected the Agency's conclusion that the pediatric study requirements were waived for pre-menarchal females and that the pediatric study requirements were met for post-menarchal adolescents, rather than stating that the Agency was waiving the requirements for all pediatric age groups.

As currently required by the Pediatric Research Equity Act (PREA),[126] certain applications or supplemental applications must include pediatric assessments of the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric

[125] Carlsson et al., supra n. 49.
[126] Section 505B of the FD&C Act (21 U.S.C. 355c).

subpopulations, unless that requirement is waived or deferred.[127] In accordance with PREA, when FDA reviewed the S-020 efficacy supplement, a partial waiver was granted for pediatric studies in pre-menarchal females because pregnancy does not occur in premenarchal females. We also determined that the applicant had fulfilled the pediatric study requirement in post-menarchal adolescents. This determination was based on data extrapolated from adults and information in literature. Review of these findings found the safety and efficacy in this population to be similar to the safety and efficacy in the adult population.[128] Therefore, we do not agree that a formal study is required in patients under 18.

With regard to your concerns about repeat abortions and your assertion that a study is necessary in this population, we acknowledge that published data concerning adverse reproductive health outcomes in U.S. women who undergo repeat medical abortions are limited. We concluded in our 2016 review of the S-020 efficacy supplement that there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. We also noted that return to fertility after the use of mifepristone is well documented. [129] This is reflected both in Section 17 of the approved labeling, Patient Counseling Information, which states that the provider should "inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses," and in the Medication Guide, which states "You can become pregnant again right after your pregnancy ends." Although you state that more than one out of every three abortions in the United Sates is a repeat abortion (Petition at 14),[130] we are not aware of reports suggesting greater safety concerns in repeat abortions than a first-time abortion. Therefore, we do not agree that a study is necessary in this population. You also cite a published study, using a mouse model, of repeated medical termination of pregnancy that showed repeat medical abortion impaired the reproductive function of female mice (Petition at 14).[131] Per our 2016 review, there is no evidence in available clinical data that repeated medical or surgical abortion is unsafe, or that fertility is impaired by the use of mifepristone; therefore, data from a single non-clinical study in mice are not persuasive.[132]

With respect to your request for a formal study of mifepristone for medical abortion in women without access to emergency care, we disagree that such a study is necessary. In order to become a certified prescriber, a healthcare provider must agree that they have the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others, and that they have the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. These prescriber qualifications ensure that mifepristone is prescribed to women for whom emergency care is available.

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[127] Section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2)).
[128] 2016 Clinical Review, supra n. 13, at 74-76.
[129] Id. at 47.
[130] In support of this assertion, you cite Jones R, Jerman J, Ingerick M. Which abortion patients have had a prior abortion? Findings from the 2014 U.S. Abortion Patient Survey. J Womens Health.
[131] Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. PLoS One. 2012;7(10):e48384. doi:10.1371/journal.pone.0048384.
[132] 2016 Clinical Review, supra n. 13, at 47.

Finally, you assert that FDA should require a formal study in patients who self-administer misoprostol. As explained in section II.A.2.b.ii of this response, FDA conducted a literature review of self-administration of misoprostol at home as part of its review of the S-020 efficacy supplement and found no safety or efficacy concerns with home self-administration of misoprostol. Therefore, we disagree that a formal study is required in this population.

With regard to safety generally, in addition to the FAERS data provided above (see section II.B.1.c.ii. in this response), FDA routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy through 70 days gestation. We have not identified any new safety concerns with the use of mifepristone for this indication.

3. Other Articles

In your Petition, you reference several documents that discuss alternative models of providing abortion medications and advocate for the lifting of the REMS on mifepristone (Petition at 23-24). You assert that these recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex.[133]
We agree that the overarching message in the publications you reference appears to be advocating self-management of medical abortion. Nonetheless, as discussed in this response, we have determined that the Mifepristone REMS Program continues to be necessary for the safe use of this drug product, with some modifications.

III. CONCLUSION

For the reasons set forth above, we deny your request that FDA restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000; and we grant in part and deny in part your request to retain the Mifepristone REMS Program. As with all approved drug products, we will continue to monitor the safety of mifepristone for the approved indication and take any appropriate actions.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2021.12.16 15:05:41 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[133] You also reference clinical trials relating to the use of mifepristone for spontaneous miscarriage management and question the results of studies related to this use (Petition at 16-18). The use of mifepristone for the management of early miscarriage is not an approved indication for this drug product and is outside the scope of the Mifepristone REMS Program. Therefore, we do not address it in this response.