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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF WASHINGTON

STATE OF WASHINGTON; STATE OF OREGON; STATE OF ARIZONA; STATE OF COLORADO; STATE OF CONNECTICUT; STATE OF DELAWARE; STATE OF ILLINOIS; ATTORNEY GENERAL OF MICHIGAN; STATE OF NEVADA; STATE OF NEW MEXICO; STATE OF RHODE ISLAND; and STATE OF VERMONT, Plaintiffs, v. UNITED STATES FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, in his official capacity as Commissioner of Food and Drugs; UNITED STATES	NO. COMPLAINT

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DEPARTMENT OF HEALTH AND HUMAN SERVICES; and XAVIER BECERRA, in his official capacity as Secretary of the Department of Health and Human Services,

Defendants.

I. INTRODUCTION

1. The availability of medication abortion has never been more important. As states across the country have moved to criminalize and civilly penalize abortion, the Plaintiff States have preserved the right to access abortion care, and have welcomed people from other states who need abortion care. The extremely limited availability of abortion in other states, and the growing threat to abortion access nationwide, makes patients' access to medication abortion paramount. Medication abortion through a combination of mifepristone and misoprostol is the "gold standard" for early termination of pregnancy, used by the majority of people in the U.S. who choose to have an abortion.

2. More than 22 years ago, the United States Food and Drug Administration (FDA) approved mifepristone (under the brand name Mifeprex) to be used with the drug misoprostol, in a two-drug medication regimen to end an early pregnancy. Approval was based on a thorough and comprehensive review of the scientific evidence, which established that mifepristone is safe and effective.

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3. Since this regimen was approved in 2000, mifepristone has been used approximately 5.6 million times in the United States.[1] As FDA acknowledged in 2016, mifepristone "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."[2] Mifepristone is safer than many other common drugs FDA regulates, such as Viagra and Tylenol.

4. Medication abortion is now the most common method of abortion in the United States. For example, almost 60% of abortions in Washington State are medication abortions.

5. But FDA has continued to hamper access by singling out mifepristone—and the people in the Plaintiff States who rely on it for their reproductive health care—for a unique set of restrictions known as a Risk Evaluation and Mitigation Strategy (REMS). The restrictions on mifepristone are a particularly burdensome type of REMS known as Elements to

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[1]FDA, Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2022, https://www.fda.gov/media/164331/download ("Mifepristone U.S. Post-Marketing Adverse Events"), attached hereto as Ex. A.

[2]FDA, Ctr. for Drug Evaluation & Research, No. 020687Orig1s020, Mifeprex Medical Review(s) at 12 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf ("FDA 2016 Medical Review"), attached hereto as Ex. B.

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Assure Safe Use (ETASU), which strictly limit who can prescribe and dispense the drug. FDA's decision to continue these burdensome restrictions in January 2023 on a drug that has been on the market for more than two decades with only "exceedingly rare" adverse events has no basis in science. It only serves to make mifepristone harder for doctors to prescribe, harder for pharmacies to fill, harder for patients to access, and more burdensome for the Plaintiff States and their health care providers to dispense.[3] Not only that, but the REMS require burdensome documentation of the patient's use of mifepristone for the purpose of abortion, making telehealth less accessible and creating a paper trail that puts both patients and providers in danger of violence, harassment, and threats of liability amid the growing criminalization and outlawing of abortion in other states.

6. FDA has imposed REMS for only 60 of the more than 20,000[4] FDA-approved prescription drug products marketed in the U.S. These cover dangerous drugs such as fentanyl and other opioids, certain risky cancer drugs, and high-dose sedatives used for patients with psychosis.[5]

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[3]Ex. B (FDA 2016 Medical Review) at 47.

[4]Office of the Commissioner, *FDA at a Glance: FDA Regulated Products and Facilities*, FDA (Nov. 2021), https://www.fda.gov/media/154548/download.

[5]*Id.*

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7. This case is about whether it is improper and discriminatory for FDA to relegate mifepristone—a medication that has been used over 5 million times with very low rates of complications, very high rates of efficacy, and which is critical to the reproductive rights of the Plaintiff States' residents, as well as visitors who travel to the Plaintiff States to seek abortion care—to the very limited class of dangerous drugs that are subject to a REMS.

8. The Plaintiff States seek an order directing FDA to follow the science and the law. The Court should order FDA to remove the unnecessary January 2023 REMS restrictions that impede and burden patients' access to a safe, proven drug that is a core element of reproductive health care in the Plaintiff States.

II. JURISDICTION AND VENUE

9. The Court has subject matter jurisdiction under 28 U.S.C. § 1331, as this is a civil action arising under federal law, and under 5 U.S.C. § 702, as this is a civil action seeking judicial review of a final agency action.

10. This action for declaratory and injunctive relief is authorized by 28 U.S.C. §§ 2201 and 2202, by Federal Rules of Civil Procedure 57 and 65, and by the inherent equitable powers of this Court.

11. The Court has personal jurisdiction over Defendants pursuant to 28 U.S.C. § 1391(e) because Defendants are agencies and officers of the United States.

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12. Venue is proper in this district pursuant to 28 U.S.C. § 1391(a) because this is a judicial district in which Plaintiff State of Washington resides. Defendants' policies adversely affect the health and welfare of residents in the Plaintiff States, including in this district, and harm the financial interests of the Plaintiff States, including Washington. Abortion access is far more limited in Eastern Washington than in Western Washington, with the State's clinics concentrated in urban areas and the I-5 corridor.

III. PARTIES

Washington

13. The Attorney General is the chief legal adviser to the State. The Attorney General's powers and duties include acting in federal court on behalf of the State on matters of public concern.

14. As an operator of medical facilities that provide reproductive health care services and pharmacies that dispense mifepristone, Washington is directly subject to the January 2023 REMS and has standing to vindicate its proprietary interests in delivering high-quality patient care.

15. Washington also has standing because the 2023 REMS creates and maintains substantial and costly administrative burdens for State-operated hospitals, clinics, and pharmacies.

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16. Washington additionally brings this suit in its capacity as parens patriae to protect its quasi-sovereign interest in the health and well-being of Washington residents.

Oregon

17. Plaintiff State of Oregon is represented by its Attorney General, who is the chief law officer for the State. Oregon has a strong interest in the proper provision of health care within the state, particularly at public hospitals, and joins in its capacity as parens patriae to protect its quasi-sovereign interest in the health and well-being of Oregon residents.

Arizona

18. The Attorney General is the chief legal adviser to the State. The Attorney General's powers and duties include acting in federal court on behalf of the State on matters of public concern.

19. As the operator of facilities that provide reproductive health care and pharmaceutical services, Arizona is directly subject to the January 2023 REMS and has standing to vindicate it proprietary interests in delivering high-quality patient care.

20. Arizona also has standing because the 2023 REMS create and maintain substantial and costly administrative burdens for health care and pharmaceutical services provided in state owned or operated facilities.

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21. Arizona additionally brings this suit in it capacity as parens patriae to protect its quasi-sovereign interest in the health and well-being of Arizona residents.

Colorado

22. Plaintiff the State of Colorado is a sovereign state of the United States of America. This action is brought on behalf of the State of Colorado by Attorney General Phillip J. Weiser, who is the chief legal representative of the State of Colorado, empowered to prosecute and defend all actions in which the state is a party. Colo. Rev. Stat. § 24-31-101(1)(a).

Connecticut

23. The State of Connecticut is a sovereign state. The Attorney General is Connecticut's chief civil legal officer, responsible for supervising and litigating all civil legal matters in which Connecticut is an interested party, including federal court matters.

24. Medication abortion is indispensable to reproductive health care in Connecticut. According to the Centers for Disease Control, more than 65% of Connecticut abortions are medication abortions using mifepristone.

25. Access to mifepristone for medicated abortions is increasingly critical in Connecticut. An ongoing wave of hospital closures and consolidations threaten to leave swaths of the state without access to on-site reproductive

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healthcare, even as demand for abortion care has increased in the aftermath of *Dobbs*.

26. Connecticut is directly subject to the January 2023 REMS and has standing to vindicate its proprietary interests in delivering high-quality patient care. Connecticut funds and operates the John Dempsey Hospital of the University of Connecticut Health Center (UConn Health) and its associated pharmacy. The Hospital provides reproductive health services, including prescribing mifepristone for medication abortions. The pharmacy dispenses mifepristone to patients.

27. Connecticut also has standing because the 2023 REMS create and maintain substantial and costly administrative burdens, including burdens to UConn Health and its associated pharmacy.

28. Connecticut additionally brings this suit in its capacity as parens patriae to protect is quasi-sovereign interest in the health and well-being of Connecticut residents.

Delaware

29. Plaintiff the State of Delaware is a sovereign state of the United States of America. This action is brought on behalf of the State of Delaware by Attorney General Kathleen Jennings, the "chief law officer of the State." *Darling Apartment Co. v. Springer*, 22 A.2d 397, 403 (Del. 1941).

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Attorney General Jennings also brings this action on behalf of the State of Delaware pursuant to her statutory authority. Del. Code Ann. tit. 29, § 2504.

Illinois

30. Plaintiff the State of Illinois is a sovereign state of the United States of America. This action is brought on behalf of the State of Illinois by Attorney General Kwame Raoul, the State's chief legal officer. *See* Ill. Const. art. V, § 15; 15 ILCS 205/4.

31. Illinois has standing because the 2023 REMS create barriers to accessing medically necessary abortion and miscarriage care, leading to subsequent health care costs, including emergency care, some of which is borne by the state through Medicaid expenditures.

32. Illinois additionally brings this suit in its capacity as *parens patriae* to protect its quasi-sovereign interest in the health and well-being of Illinois residents.

Attorney General of Michigan

33. Attorney General Dana Nessel is the chief legal adviser to the State of Michigan. The Attorney General's powers and duties include acting in federal court on behalf of the State on matters of public concern.

34. The Attorney General brings this suit in her capacity as parens patriae to protect its quasi-sovereign interest in the health and well-being of Michigan residents.

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Nevada

35. Plaintiff State of Nevada is represented by its Attorney General. The Attorney General is the chief legal officer of the State.

36. The Nevada Attorney General may commence or defend a suit in state or federal court when in his opinion a suit is necessary to protect and secure the interest of the State.

37. Nevada provides reproductive healthcare services including medication abortions using mifepristone.

38. As a provider of reproductive healthcare services, Nevada is subject to the January 2023 REMS program.

39. Nevada has standing to challenge the REMS because it imposes financial and administrative burdens on Nevada reproductive healthcare service providers seeking to prescribe and distribute mifepristone for medication abortions.

40. Nevada also has standing to challenge the program because the program interferes with its inherent authority to provide for the health and welfare of its residents. It imposes medically unnecessary barriers to Nevada's provision of reproductive healthcare using the least intrusive and most cost-effective means.

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New Mexico

41. Plaintiff State of New Mexico, represented by and through its Attorney General, is a sovereign state of the United States of America. Attorney General Raúl Torrez is the chief legal officer of the State of New Mexico. He is authorized to prosecute all actions and proceedings on behalf of New Mexico when, in his judgment, the interest of the State requires such action. N.M. Stat. Ann. § 8-5-2(B). Likewise, he shall appear before federal courts to represent New Mexico when, in his judgment, the public interest of the state requires such action. N.M. Stat. Ann. § 8-5-2(J). This challenge is brought pursuant to Attorney General Torrez's statutory authority.

42. As an operator of medical facilities that provide reproductive health care services and pharmacies that dispense mifepristone, New Mexico is directly subject to the 2023 REMS and has standing to vindicate its proprietary interests in delivering high-quality patient care.

43. New Mexico also has standing because the 2023 REMS will impose substantial and costly administrative burdens for State-operated hospitals, clinics, and pharmacies.

44. New Mexico additionally brings this suit in its capacity as parens patriae to protect its quasi-sovereign interest in the health and well-being of New Mexico residents.

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Rhode Island

45. The Rhode Island Attorney General is the chief legal officer for the State of Rhode Island. The Rhode Island Attorney General's powers and duties include acting in federal court on behalf of the State on matters of public concern.

46. Rhode Island has standing because the 2023 REMS create barriers to accessing medically necessary abortion and miscarriage care, leading to subsequent health care utilization, including emergency care, some cost of which is borne by the state through Medicaid expenditures.

47. Rhode Island additionally brings this suit in its capacity as parens patriae to protect its quasi-sovereign interest in the health and well-being of Rhode Island residents.

Vermont

48. The Attorney General is the chief legal adviser to the State. The Attorney General's powers and duties include representing the State in civil causes when, in her judgment, the interests of the State so require.

49. Vermont brings this suit in its capacity as parens patriae to protect its quasi-sovereign interest in the health and well-being of Vermont residents.

Plaintiff States

50. The Plaintiff States collectively represent more than 59 million Americans with protected rights to abortion care.

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Defendants

51. Defendant United States Food and Drug Administration (FDA) is an agency of the federal government within the United States Department of Health and Human Services (HHS). FDA is responsible for administering the provisions of the federal Food, Drug, and Cosmetic Act that are relevant to this Complaint.

52. Robert M. Califf is the Commissioner of the United States Food and Drug Administration and is sued in his official capacity. He is responsible for administering FDA and its duties under the federal Food, Drug, and Cosmetic Act.

53. Defendant HHS is a federal agency within the executive branch of the federal government.

54. 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 FDA.

IV. ALLEGATIONS

A. Statutory Background

55. Under the Food, Drug and Cosmetic Act (FDCA), a new drug cannot be marketed and prescribed until it undergoes a rigorous approval process to determine that it is safe and effective. *See generally* 21 U.S.C. § 355. An approved prescription medication is subject to robust safeguards to ensure that it is used safely and appropriately, including the requirement of a prescription by a

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licensed medical provider, patient informed-consent laws, scope of practice laws, professional and ethical guidelines, and state disciplinary laws regulating the practice of medicine and pharmacy, as well as additional warnings, indications, and instructions that FDA may impose specific to the medication.

56. FDA relies on this set of safeguards to ensure the safe and effective use of the *vast* majority of prescription drugs.

57. A "Risk Evaluation and Mitigation Strategy" (REMS) is an additional set of requirements, beyond the usual network of safeguards, that FDA may impose in the rare case when—and only when—"necessary to ensure that the benefits of the drug outweigh the risks of the drug[.]" 21 U.S.C. § 355-1(a)(1).

58. The most burdensome type of REMS are "Elements to Assure Safe Use" (ETASU), which FDA may impose only when necessary because of a drug's "inherent toxicity or potential harmfulness." *Id.* § 355-1(f)(1).

59. By statute, FDA may impose ETASU only for medications that demonstrate risks of serious side effects such as death, incapacity, or birth defects, and only where the risk of side effects is sufficiently severe that FDA could not approve, or would have to withdraw approval of, the medication, absent the ETASU. *Id.* §§ 355-1(b)(5), (f)(1)(A).

60. ETASU must not be "unduly burdensome on patient access to the drug, considering in particular . . . patients in rural or medically underserved

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areas," and must "minimize the burden on the health care delivery system[.]" *Id.* §§ 355-1(f)(2)(C)–(D).

61. In light of these stringent statutory limitations, REMS, and in particular an ETASU, are exceptionally rare: of the more than 20,000 prescription drug products approved by FDA and marketed in the U.S.,[6] there are only 60 REMS in place, 56 of which include an ETASU, covering dangerous drugs like fentanyl and other opioids.[7]

B. FDA's Approval of Mifepristone and the History of the Mifepristone REMS Program

62. The current FDA-approved regimen for the medical termination of early pregnancy involves two drugs: (1) *mifepristone*, which interrupts early pregnancy by blocking the effect of progesterone, a hormone necessary to maintain a pregnancy, and (2) *misoprostol*, which causes uterine contractions that expel the pregnancy from the uterus. Shortly after taking mifepristone and then misoprostol, a patient will experience a miscarriage.[8]

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[6] *Supra* n.5.

[7] Ex. C (FDA Approved REMS).

[8] Taken alone, misoprostol also acts as an abortifacient—but it is less effective and causes more negative side effects than the mifepristone/misoprostol regimen. Misoprostol, however, it is not subject to a REMS; patients may obtain it from any provider and have it filled at retail or mail-order pharmacies.

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63. Mifepristone was first approved for medical termination of early pregnancy in France in 1988 and its approval expanded to the United Kingdom and European countries throughout the 1990s.

64. In 1996, the Population Council, a non-profit organization based in the United States, sponsored a New Drug Application (NDA) for Mifeprex for use in combination with misoprostol for the medical termination of early pregnancy. In 1999, the Population Council contracted with Danco Laboratories, L.L.C. (Danco) to manufacture and market the medication.

65. FDA approved the marketing of mifepristone under the brand name Mifeprex in September 2000,[9] concluding that mifepristone is safe and effective for medical termination of intrauterine pregnancy through 49 days' gestation when used in a regimen with the already-approved drug, misoprostol. In granting its approval, FDA extensively reviewed the scientific evidence and determined that mifepristone's benefits outweigh any risks.[10]

66. FDA's review included three clinical trials that together involved 4,000 women: two French trials that were complete at the time of the application, and one then-ongoing trial in the United States for which summary data on

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[9]FDA NDA 20-687 Approval Memo, Sept. 28, 2000, attached hereto as Ex. D.

[10]Food and Drug Administration Approval and Oversight of the Drug Mifeprex, https://www.gao.gov/assets/gao-08-751.pdf, attached hereto as Ex. E.

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serious adverse events were available.[11] FDA has explained that "[t]he data from these three clinical trials . . . constitute substantial evidence that Mifeprex is safe and effective for its approved indication in accordance with the [FDCA]."[12] FDA also considered: (1) results from other European trials from the 1980s and 1990s in which mifepristone was studied alone or in combination with misoprostol or similar drugs; (2) a European postmarket safety database of over 620,000 women who used medication to terminate a pregnancy, approximately 415,000 of whom had received a mifepristone/misoprostol regimen[13]; and (3) data on the drug's chemistry and manufacturing.[14]

67. Despite the strong findings on the safety and efficacy of Mifeprex from clinical trials and European post-market experience, FDA originally approved Mifeprex under Subpart H of the FDCA regulations (the predecessor to the REMS statute) and imposed "restrictions to assure safe use"—a restricted

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[11] *Id.* at 5.

[12] 2016 FDA Letter to Am. Ass'n of Pro-Life Obstetricians & Gynecologists, Christian Medical & Dental Ass'ns, and Concerned Women for Am. denying 2002 Citizen Petition, Docket No. FDA-2002-P0364 (Mar. 29, 2016) (Citizen Petition Denial) at 8, Mar. 29, 2016, attached hereto as Ex. F.

[13] *Id.* at 8.

[14] Ex. E, supra n.11.

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distribution system—as a condition of approval.[15] For example, FDA imposed an in-person dispensing requirement (later "ETASU C," pursuant to 21 U.S.C. § 355-1(f)(3)(C)) and permitted the drug to be dispensed only in a hospital, clinic, or medical office, by or under the supervision of a "certified provider" (discussed more below), who at that time could only be a physician. FDA also imposed a prescriber-certification ETASU (later "ETASU A," pursuant to 21 U.S.C. § 355-1(f)(3)(A)), which prohibited health care providers from prescribing the drug unless they first attested to their clinical abilities in a signed form kept on file by the manufacturer, and agreed to comply with reporting and other REMS requirements. FDA also imposed a Patient Form ETASU (later "ETASU D," pursuant to 21 U.S.C. § 355-1(f)(3)(D)), requiring the prescriber and patient to review and sign a special form with information about the mifepristone regimen and risks, and required the prescriber to provide the patient with a copy and place a copy in the patient's medical record. The same information contained in the patient form is also included in the "Medication Guide" that is part of the FDA-approved labeling provided to patients with mifepristone.

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[15] Although the Subpart H regulations are sometimes referred to as FDA's "accelerated approval" regulations, FDA has explained elsewhere that its 2000 approval of Mifeprex, which occurred more than four years after the new drug application was submitted to FDA, did not involve an accelerated review.

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68. FDA's decision to subject Mifeprex to an ETASU under Subpart H was highly unusual. In the fifteen years from 1992 (the year the Subpart H regulations were promulgated) to February 2007 (just before the creation of the REMS statute), only seven NDAs, including Mifeprex, were approved subject to ETASU under Subpart H.[16] By comparison, FDA approved 961 NDAs with no additional restrictions in the roughly thirteen years from January 1993 to September 2005.[17]

69. The Food and Drug Administration Amendments Act of 2007 effectively replaced Subpart H of the FDCA regulations with the REMS statute. All drugs previously approved under Subpart H—including Mifeprex—were deemed by the Amendments Act to have a REMS in place. Following passage of the 2007 FDCA, Mifeprex continued to be subject to the same ETASU as before.

70. In 2011, FDA issued a new REMS for Mifeprex incorporating the same restrictions under which the drug was approved eleven years earlier.

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[16] *Id.* at 27.

[17] U.S. Gov't Accountability Off., *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49, 20 (Nov. 2006), http://www.gao.gov/assets/gao-07-49.pdf.

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71. In 2013, FDA reviewed the existing REMS and reaffirmed the restrictions already in place.[18]

72. In May 2015, Mifeprex's manufacturer (Danco) submitted a supplemental NDA proposing to update the label to reflect evidence-based practice across the country—mainly, the use of 200 mg of mifepristone instead of 600 mg. In July 2015, Danco also submitted its statutorily required REMS assessment, proposing minor modifications.

73. This submission prompted a review of the Mifeprex label and REMS by FDA in 2015-2016. As part of that review, FDA received letters from more than 40 medical experts, researchers, advocacy groups, and professional associations who asked, *inter alia*, that the REMS be eliminated in their entirety.

74. Signatories requesting that FDA eliminate the Mifeprex REMS included the American College of Obstetricians and Gynecologists (ACOG), the leading professional association of physicians specializing in the health care of women, which represents 58,000 physicians and partners in women's health; the American Public Health Association (APHA), the nation's leading public health organization; the Director of Stanford University School of Medicine's Division of Family Planning Services and Research; the Chair of the Department of Obstetrics and Gynecology at the University of New Mexico School of Medicine;

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[18]FDA Final Risk Evaluation and Mitigation Strategy (REMS) Review (Oct. 10, 2013), attached hereto as Ex. G.

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and the Senior Research Demographer in the Office of Population Research at Princeton University.

75. As one letter explained: "Although the FDA may have decided 15 years ago that the balance of risk and burden came out in favor of restricting mifepristone's indicated use and distribution, today both science and the current conditions surrounding patient access to abortion care call strongly for a reevaluation of the mifepristone label and REMS restrictions, especially its Elements to Assure Safe Use (ETASU)."[19] In asking FDA to "[e]liminate the REMS and ETASU for mifepristone," the letter specifically asked FDA to, among other things, (i) "[e]liminate the Prescriber Agreement certification requirement" and (ii) "remove the confusing and unnecessary Patient Agreement."[20]

76. The signatory organizations explained that the Prescriber Agreement certification requirement should be eliminated, because, among other things[21]:

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[19]Letter from SFP, *et al.*, to Stephen Ostroff, M.D., Robert M. Califf, M.D., & Janet Woodcock, M.D., 1 (Feb. 4, 2016) (SFP Letter to FDA), attached hereto as Ex. H.

[20]*Id.* at 2–4.

[21]*Id.* at 3.

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a. "*The Prescriber's Agreement is unnecessary for the safe dispensation of mifepristone*. . . . [H]ealth care professionals are already subject to many laws, policies, and ordinary standards of practice that ensure they can accurately and safely understand and prescribe medications. Provider certification is not required for health care professionals to dispense other drugs, including drugs that carry black box, or boxed, warnings about their medical risks. Accutane, for example, has a boxed warning that describes the potential risks of the drug, but Accutane prescribers are not required to submit a certification form in order to prescribe it. Mifeprex also has a boxed warning and there is no medical reason for a Prescriber's Agreement to be required in addition."

b. "*The Prescriber's Agreement forces providers to identify themselves as abortion providers to a centralized entity (Danco Laboratories) inspected and regulated by the FDA, which could discourage some from offering medication abortion care to their patients*. In 2014, more than half of U.S. health care facilities that provide abortions (52%) experienced threats and other types of targeted intimidation, and one in five experienced severe violence, such as blockades, invasions, bombings, arsons, chemical attacks, physical violence, stalking, gunfire, bomb threats, arson threats, or death threats. Robert Dear's November 27, 2015, standoff at a Planned Parenthood health center in Colorado, which resulted in three deaths, provides one recent and chilling example of anti-abortion violence. Given such escalating harassment and violence against known abortion providers, clinicians may be understandably reluctant to add their names to a centralized database of mifepristone providers."

c. "*The Prescriber's Agreement would be incompatible and unnecessary if there were an expanded distribution system*. If dispensing venues are expanded as proposed . . . ordinary standards of practice and state regulations would govern pharmacists' and providers' distribution of mifepristone, and a specific certification process would be unnecessary. Furthermore, a distribution system that incorporates the Prescriber's Agreement would be extremely difficult to maintain as a practical matter. Pharmacists would need to check the certification status of each prescriber before filling a prescription, which they do not normally have to do when filling other prescriptions."

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77. The organizations also argued that the Patient Agreement was unnecessary, explaining: "This requirement is medically unnecessary and interferes with the clinician-patient relationship. It should be eliminated entirely."[22]

78. The letter also urged FDA to "[c]onsider the current legal and social climate," explaining that "[t]he overall legal and social climate around abortion care intensifies all of the burdens that the mifepristone REMS places on patients and makes it even more critical that the FDA lift medically unnecessary restrictions on the drug."[23] The letter concludes:

> Mifepristone continues to hold immense promise for patient access to a safe and effective early abortion option, but medically unnecessary regulations are impeding its full potential. Extensive scientific and clinical evidence of mifepristone's safety and efficacy, and the ever-increasing burden on patient access to abortion care, clearly demonstrate that mifepristone's REMS program is not needed to protect patients. In light of the FDA's statutory mandate from Congress to consider the burden caused to patients by REMS, and the agency's own stated commitment to ensuring that the drug restrictions do not unduly burden patient access, we ask that the FDA lift mifepristone's REMS . . . .[24]

79. FDA summarized these "Advocacy Group Communications" as follows:

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[22] *Id.* at 4.

[23] *Id.* at 5.

[24] *Id.* at 6.

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> The Agency received three letters from representatives from academia and various professional organizations . . . . In general, these advocates requested FDA to revise labeling in a manner that would reflect current clinical practice, including the new dose regimen submitted by the Sponsor, and proposing to extend the gestational age through 70 days. Other requests were that the labeling not require that the drug-taking location for both Mifeprex and misoprostol be restricted to the clinic, and that labeling not specify that an in-person follow-up visit is required. The advocates also requested that any licensed healthcare provider should be able to prescribe Mifeprex and that the REMS be modified or eliminated, to remove the Patient Agreement and eliminate the prescriber certification, while allowing Mifeprex to be dispensed through retail pharmacies.[25]

80. A multidisciplinary FDA review team considered the requested changes. This review concluded that "no new safety concerns have arisen in recent years, and that the known serious risks occur rarely," and that "[g]iven that the numbers of . . . adverse events appear to be stable or decreased over time, it is likely that . . . serious adverse events will remain acceptably low."[26]

81. Following the multidisciplinary review team's analysis, FDA made several changes to Mifeprex's indication, labeling, and REMS. Relying on safety and efficacy data from multiple studies, FDA increased the gestational age limit from 49 to 70 days.[27] FDA also reduced the number of required in-person clinic

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[25]FDA, Ctr. for Drug Evaluation & Research, 020687Orig1s020, Cross Discipline Team Leader Review 25 (Mar. 29, 2016), attached as Ex. I.

[26]Ex. B (FDA 2016 Medical Review) at 9, 39, 47, 49.

[27]The overwhelming majority (80%) of abortions occur within the first 70 days (10 weeks) of pregnancy. Katherine Kortsmit, et al., *Abortion Surveillance*

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visits to one (whereas patients had previously been required to visit a clinic setting twice in order to receive the medication). FDA determined that at-home administration of misoprostol is safe because multiple studies showed that administration of the drug was "associated with exceedingly low rates of serious adverse events" and because administering misoprostol at home would more likely result in patients being in an "appropriate and safe location" when cramping and bleeding caused by the drug would begin.[28] FDA also found no significant difference in outcomes based on whether patients had follow-up appointments via phone call or in-person or based on the timing of those appointments. Additionally, FDA allowed a broader set of healthcare providers, rather than only physicians, to prescribe mifepristone, finding no serious risk to patients from expanding the types of healthcare providers who could become

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– *United States, 2020*, 71 CDC Morbidity & Mortality Weekly Report 10 at 12 (Nov. 25, 2022), https://www.cdc.gov/mmwr/volumes/71/ss/pdfs/ss7110a1-H.pdf.

[28]U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Mifeprex Summary Review at 15 (Mar. 29, 2016) (2016 Summary Review), attached hereto as Ex. J.

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certified under the 2016 REMS.[29] But FDA still required that mifepristone, the first drug in the regimen, be administered in a clinic setting.

82. In addition, FDA expert review team and the Director of FDA's Center for Drug Evaluation and Research recommended eliminating the Patient Agreement Form because it contains "duplicative information already provided by each healthcare provider or clinic," "does not add to safe use conditions," and "is a burden for patients."[30] But they were overruled by the FDA Commissioner, who directed the Form be retained.[31] FDA retained the in-person dispensing requirement and provider certification as well.

83. In 2019, FDA approved a different manufacturer's abbreviated new drug application for a generic version of mifepristone. When it approved the

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[29]U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Mifeprex REMS (Mar. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf (hereinafter 2016 REMS).

[30]Ex. J (2016 Summary Review) at 25.

[31]U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Mifeprex Risk Assessment and Risk Mitigation Review(s): Letter from Janet Woodcock, M.D., Ctr. for Drug Evaluation & Research, Regarding NDA 020687, Supp 20, 1 (Mar. 28, 2016) (hereinafter "Woodcock Patient Agreement Memo"), attached hereto as Ex. K.

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abbreviated NDA, FDA also established the Mifepristone REMS Program, which covers both Mifeprex and the generic.

84. In May 2020, the American College of Obstetricians and Gynecologists sued FDA, challenging the Mifepristone REMS Program's in-person dispensing requirement in light of the COVID-19 pandemic. *See Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183 (D. Md. 2020), *stayed by FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578, 578 (2021) (mem.). Over FDA's objection that "based on FDA's scientific judgment, the In-Person Requirements are necessary to assure safe use of mifepristone and thus to protect patients' safety," *id.* at 228, the U.S. District Court for the District of Maryland preliminarily enjoined the in-person dispensing requirements, allowing healthcare providers to forgo it based on their medical judgment for the duration of the declared COVID-19 public health emergency. *Id.* at 233.

85. In April 2021, FDA suspended the in-person dispensing requirement during the COVID-19 public health emergency because, during the six-month period in which the in-person dispensing requirement had been enjoined, the availability of mifepristone by mail showed no increases in serious patient safety concerns. Thereafter, FDA commenced a formal REMS review.

86. Finally, on January 3, 2023, FDA modified the REMS by, *inter alia*, removing the in-person dispensing requirement entirely. However, as discussed

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further below, the Mifepristone REMS continue to impose both the Prescriber Agreement Form and the Patient Agreement Form. The 2023 REMS also added a new pharmacy-certification requirement.[32]

C. The Safety of Mifepristone

87. Mifepristone is extremely safe and effective for terminating early pregnancies.

88. As discussed above, FDA's approval of mifepristone in 2000 rested on a comprehensive evaluation of the scientific data, and FDA reasonably determined, in its expert judgment, that the evidence showed mifepristone is safe and effective for abortion of early pregnancy.

89. When FDA conducted another medical review of mifepristone in 2016 (based on the then 2.5 million uses of Mifeprex for medication abortion in the U.S. since the drug's 2000 approval) it found: "[Mifeprex] 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

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[32]FDA Risk Evaluation and Mitigation Strategy (REMS) Single Shared System for Mifepristone 200 MG (2023 REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2023_01_03_REMS_Full.pdf, attached hereto as Ex. L.

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rare."[33] FDA observed at that time that "[m]ajor adverse events . . . 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."[34] The Agency further stated that "[t]he safety profile of Mifeprex is well-characterized and its risks well-understood after more than 15 years of marketing. Serious adverse events are rare and the safety profile of Mifeprex has not substantially changed."[35] Since that 2016 medical review, mifepristone has

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[33]Ex. B (FDA 2016 Medical Review) at 12; *see also* U.S. Food & Drug Admin., Full Prescribing Information for Mifeprex 7–8, Tables 1 & 2 (approved Mar. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf ("Mifeprex Labeling"), attached hereto as Ex. M.

[34]Ex. B (FDA 2016 Medical Review) at 47 (emphasis added); *see also* Ex. M (Mifeprex Labeling) at 8, Table 2; *see also* Kelly Cleland et al., Significant Adverse Events and Outcomes After Medical Abortion, 121 OBSTETRICS & GYNECOLOGY 166, 166 (2013) ("Medical research has consistently demonstrated that mifepristone is safe and effective and that adverse events and outcomes are exceedingly rare, occurring in less than a fraction of 1% of cases.").

[35]U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Mifeprex Risk Assessment and Risk Mitigation Review(s):

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been used an additional 3 million times in the United States for medication abortion.

90. From the time mifepristone was approved in 2000, there have only been 28 reported associated deaths out of 5.6 million uses—an associated fatality rate of .00005%.[36] Further, FDA acknowledges that *none* of these deaths can be causally attributed to mifepristone. The 28 reported deaths were included in the adverse events summary "regardless of causal attribution to mifepristone" and included cases of homicide, drug overdose, ruptured ectopic pregnancy, and sepsis (a life-threatening immune response to an infection).[37] And in its 2016 review, FDA noted that, while roughly half the deaths to that point were associated with Clostridial septic infections, "[t]here have been no Clostridial septic deaths reported in the US since 2009."[38]

91. In other cases of fatal infections associated with mifepristone, FDA has acknowledged that "the critical risk factor" is not mifepristone but

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REMS Modification Memorandum at 3 (Mar. 29, 2016) (hereinafter 2016 REMS Modification Memorandum), attached hereto as Ex. N.

[36]Ex. A (Mifepristone U.S. Post-Marketing Adverse Events Summary).

[37]*Id.*

[38]*Id.*

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"pregnancy itself," as similar infections "have been identified both in pregnant women who have undergone medical abortion and those who have not[.]"[39]

92. The specific serious complications identified in the FDA-approved labeling for Mifeprex are "Serious and Sometimes Fatal Infections or Bleeding." But the labeling specifies that such "serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion or childbirth"—in other words, any time after the pregnant uterus is emptied—and that "[n]o causal relationship between the use of MIFEPREX and misoprostol and [infections and bleeding] has been established."[40]

D. The January 2023 Mifepristone REMS

93. Despite this undisputed evidence of safety and effectiveness, FDA continues to impose a 2023 REMS with ETASU for mifepristone.

94. The current REMS was approved in January 2023 (the 2023 REMS).[41]

95. The 2023 REMS imposes three primary hurdles to accessing mifepristone. Two of these are continuing restrictions and the third is a new

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[39]Ex. F at 26 n.69.

[40]Ex. M (Mifeprex Labeling) at 2, 16.

[41]Ex. L (2023 REMS).

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restriction. Each hurdle unduly restricts mifepristone access without any corresponding medical benefit.

96. ***First***, the REMS continues to provide that mifepristone can only be prescribed by a health care provider who has undergone a "special[] certif[ication]" process in which they attest that they can accurately date a pregnancy, diagnose an ectopic pregnancy, and provide surgical intervention or referral in the event of any complications.[42] This "special certification" must be submitted to each certified pharmacy to which a provider intends to submit Mifreprex prescriptions, and must also be submitted to the distributor if a prescriber intends to dispense in-office.

97. For many healthcare providers, becoming specially certified is unduly burdensome and raises safety concerns. Some providers are deterred by the unusual step of having to become certified to prescribe the medication; others, misled by mifepristone's REMS designation, misperceive it is a dangerous medication or out of the prescriber's scope of practice; and still others are not comfortable having their names compiled in a list of medication abortion prescribers for fear that they or their families may be targeted by anti-abortion activists. This fear is particularly acute for doctors who hold medical licenses in multiple states (with abortion laws different from the Plaintiff States'), and for medical residents in the Plaintiff States who intend to eventually practice in a

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[42]Mifepristone Prescriber Agreement Forms, attached as Ex. O.

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state that heavily restricts abortion. These concerns, which FDA was made aware of as far back as 2016, are heightened now due to the growing criminalization and penalization of abortion, including laws that subject health care providers to criminal penalties and significant monetary liability.

98. ***Second***, although the 2023 REMS allows mifepristone to be dispensed directly by pharmacies (as opposed to being dispensed by a provider in a healthcare clinic, as prior REMS required), the REMS unnecessarily requires dispensing pharmacies to be "specially certified" by the drug's sponsor.[43]

99. Special certification requires pharmacies to verify that mifepristone prescriptions are written only by "certified" providers and to adhere to additional burdensome communication, recordkeeping, and training requirements beyond what is required for the vast majority of prescription drugs. Under the REMS, a pharmacy cannot dispense mifepristone to a patient until it confirms that the provider who wrote the prescription is specially certified.[44] This hurdle creates new costs and administrative burdens for pharmacies—and worse, threatens unnecessary delay patients seeking time-sensitive medication.

100. Further, by limiting mifepristone dispensing to "certified" pharmacies, the REMS requires healthcare providers to track which pharmacies are certified to dispense mifepristone, rather than allowing patients to select their

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[43]Mifepristone Pharmacy Agreement Forms, attached as Ex. P.

[44]*Id.*

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pharmacy of choice. And the reverse is true as well—pharmacies that wish to dispense mifepristone must go through the added step of confirming that each mifepristone prescription comes from a "specially certified" provider.

101. ***Third***, the 2023 REMS retains the requirement that each patient sign a Patient Agreement Form in order to receive a mifepristone prescription.[45] This form, among other things, requires a patient to certify: "I have decided to take mifepristone and misoprostol to end my pregnancy."[46] This Patient Agreement Form must be signed by both the patient and provider, a copy must be placed into the patient's medical record, and a copy must be given to the patient along with the Medication Guide.

102. This Patient Agreement Form creates significant privacy and safety issues for both patients and providers. It specifically identifies the patient as taking the medication for the purpose of ending their pregnancy—as opposed to, for instance, miscarriage management, for which the medication is also frequently prescribed. Anyone who obtains access to the patient's medical record will thus have evidence that the patient received the medication for abortion, which is a particular concern for patients who receive care from a provider in a state where abortion is legal but reside in a state where abortion is illegal. Making matters worse, for patients who receive mifepristone for miscarriage

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[45]Mifepristone Patient Agreement Form, attached as Ex. Q.

[46]*Id.*

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management, the evidence will be false. The form also identifies the provider to anyone who obtains access to the patient's medical record or sees the copy of the form that must be provided to the patient—potentially including, for example, a patient's spouse, partner, or parent. This exposes providers and patients to threats of potential violence, threats of legal liability (even when the care provided is lawful in the relevant Plaintiff State), or other life-altering consequences. On top of that, because patients who take the medication for miscarriage management are also required to sign the Patient Agreement Form, it may be traumatizing for individuals experiencing a miscarriage to nonetheless have to attest that they are "decid[ing]" to "end [their] pregnancy."

103. None of the harms caused by the Patient Agreement Form is necessary, as the information contained on the form is duplicative of the information already provided to patients in the five-page Medication Guide that accompanies mifepristone. The comprehensive Medication Guide answers questions such as: "What symptoms should I be concerned with?"; "Who should not take Mifepristone tablets?"; "What should I tell my healthcare provider before taking Mifepristone tablets?"; "How should I take Mifepristone tablets?"; and "What are the possible side effects of Mifepristone tablets?"[47] The Patient Agreement Form is also duplicative of provider counseling, as medical

[47]Mifepristone Medication Guide, attached as Ex. R.

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ethics require providers to counsel patients on the risks and benefits of all medications.

104. ***In sum***, although the 2023 REMS improved on the prior REMS by dropping the requirement to dispense mifepristone in person, the REMS nonetheless retains unduly burdensome, harmful, and unnecessary dispensing and prescribing requirements, continues to expose providers and patients to unnecessary privacy and safety risks, and creates new hurdles that further burden an already overstretched health care system.

E. The 2023 REMS Violate the FDCA

105. FDA's imposition of the burdensome 2023 REMS requirements is contrary to the FDCA.

106. As noted above, FDA may impose an ETASU on a medication only if the medication is "associated with a serious adverse drug experience," which the statute defines as one that "results in" death or "immediate risk of death," "inpatient hospitalization or prolongation of existing hospitalization," "persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions," or "a congenital anomaly or birth defect," or that "may jeopardize the patient and may require a medical or surgical intervention to prevent [such] an outcome . . . ." 21 U.S.C. §§ 355-1(f)(1)(A), (b)(4)(A)–(B). And an ETASU may be imposed only where "required . . . to mitigate a specific serious risk" of a serious adverse drug experience, and only where such risk is sufficiently severe

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that absent the ETASU, FDA would not approve or would withdraw approval of the medication. *Id.* §§ 355-1(b)(5), (f)(1)(A).

107. Mifepristone does not meet these stringent standards because it is not "associated with a serious adverse drug experience." To the contrary, FDA itself has concluded that serious adverse events following mifepristone use are "exceedingly rare."[48]

108. Since mifepristone was approved in 2000, there have been only 28 reported associated deaths out of 5.6 million uses—an associated fatality rate of .00005%. And not a single one of these deaths can be causally attributed to mifepristone.[49] By contrast, thousands of deaths have been associated with phosphodiesterase type-5 inhibitors for the treatment of erectile dysfunction (e.g., Viagra)—which are not subject to a REMS.[50] And "other drugs with higher

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[48]Ex. B (FDA 2016 Medical Review) at 47; *see also* Ex. A (Mifepristone U.S. Post-Marketing Adverse Events Summary).

[49]*Id.*

[50]Advancing New Standards in Reproductive Health , *Analysis of Medication Abortion Risk and the FDA report "Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2018"*, Mifepristone safety: Issue Brief (Apr. 2019), https://www.ansirh.org/sites/default/files/publications/files/mifepristone_safety_4-23-2019.pdf.

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complication rates, such as acetaminophen, aspirin, loratadine, and sildenafil, do not have REMS restrictions[.]"[51]

109. Moreover, the ETASU violates the FDCA's requirement that such restrictions not be "*unduly burdensome* on patient access to the drug, considering in particular . . . patients in rural or medically underserved areas," and must "minimize the burden on the health care delivery system[.]" 21 U.S.C. §§ 355-1(f)(2)(C)–(D) (emphasis added).[52]

110. As explained in more detail below, the 2023 REMS significantly burdens patient access to mifepristone without *any* appreciable safety benefits. These burdens fall particularly heavily on rural patients in the Plaintiff States because the vast majority of "specially certified" providers practice in cities. Plus, with a number of states imposing severe restrictions on access to abortion care that used to be constitutionally protected, many patients in these medically underserved areas of the country are turning to Plaintiff State providers for this care. This is particularly pronounced in Plaintiff States sharing borders with states

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[51]2018 Congress of Delegates, *Resolution No. 506 (Co-Sponsored C) – Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization on Mifepristone*, Am. Acad. Of Fam. Physicians (2019), https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf.

[52]*Supra* n.52.

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that allow little to no access—for example, in Washington, Oregon, and Nevada, which border Idaho, in Illinois, which borders Missouri and Indiana, and in New Mexico, which borders Texas. Against this backdrop, the 2023 REMS significantly and unduly burdens health care delivery in the Plaintiff States by imposing substantial, unjustified burdens on health care providers, clinics, pharmacies, and hospitals.

F. The 2023 REMS Are Unsupported by Science

111. The 2023 REMS requirements are not supported by scientific evidence.

112. First, the Patient Agreement Form remains in place even though the team of expert reviewers at FDA's Center for Drug Evaluation and Research (CDER) unanimously recommended eliminating it in 2016 because it is duplicative of informed consent laws and standards, "does not add to safe use conditions[,] . . . and is a burden for patients."[53] But this team of experts was overruled by the agency head.[54]

113. Similarly, the requirement that clinicians certify that they are competent to prescribe mifepristone provides no additional safety benefit beyond the numerous existing laws and safety standards already in place to ensure health care providers practice only within their competency. The certification

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[53]Ex. H (2016 Summary Review) at 25.

[54]Ex. I (Woodcock Patient Agreement Memo) at 1.

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requirement is also out of step with how FDA regulates other, less safe medications. Physicians are allowed to prescribe countless higher-risk drugs without first attesting to their competency to make an accurate diagnosis or provide follow-up care in the event of a complication.

114. The REMS requirement that pharmacies, too, must be "specially certified" in order to dispense mifepristone is similarly baseless. It requires pharmacies to confirm they have met the unnecessary provider-certification requirement before filling prescriptions, affords no patient safety benefits on top of the laws and standards governing the practice of pharmacy, and, instead, acts as a significant barrier to patient access to a time-sensitive medication.

115. Accordingly, the mifepristone REMS is opposed by leading medical organizations, including the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Family Physicians (AAFP), and the American Medical Association (AMA).

116. Since at least 2016, ACOG's position has been "that a Risk Evaluation and Mitigation Strategy (REMS) is no longer necessary for mifepristone, given its history of safe use. The REMS requirement is inconsistent

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with requirements for other drugs with similar or greater risks, especially in light of the significant benefit that mifepristone provides to patients."[55]

117. And since at least 2018, AAFP's position has been that the REMS restrictions "are not based on scientific evidence"; are overly burdensome on practitioners and impede patient access to care, particularly "for patients who might prefer to go to their own physician and for rural patients who have no other access points beyond their local physician"; cause "delays in care, thereby increasing second-trimester and surgical abortions, both of which have increased complication rates"; and create "a barrier to safe and effective off-label uses of mifepristone, such as for anti-corticoid treatment of Cushing's disease, term labor induction, and miscarriage management[.]"[56]

118. In a June 21, 2022, letter to FDA Commissioner Califf, ACOG and AMA urged the Agency to "eliminate the requirement for patients to sign a form to get the drug" and "lift the requirement that prescribers acquire a certification from the manufacturer," noting that "[b]arriers to accessing mifepristone do not

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[55]Advocacy and Health Policy, *ACOG Statement on Medication Abortion*, ACOG (Mar. 30, 2016) https://www.acog.org/news/news-releases/2016/03/acog-statement-on-medication-abortion.

[56]*Supra* n.52.

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make care safer, are not based on medical evidence, and create barriers to patient access to essential reproductive health care."[57]

119. Further, in 2022, ACOG, along with 48 other organizations, submitted a citizen petition to FDA seeking to add miscarriage management as an indication to the drug's label, to eliminate or modify the REMS for that use, and more generally requesting the removal of the mifepristone REMS.[58]

120. The petition asked that "the Patient Agreement Form be removed entirely because it is medically unnecessary and repetitive of informed consent, as a previous review conducted by [FDA Center for Drug Evaluation and Research] determined in 2016."[59]

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[57]Letter from Maureen G. Phipps, Am. Coll. of Obstetricians & Gynecologists, to Robert Califf, MD (Jun. 21, 2022), https://searchlf.ama-assn.org/letter/documentDownload?uri=/unstructured/binary/letter/LETTERS/lfdr.zip/2022-6-21-Joint-ACOG-AMA-Letter-to-FDA-re-Mifepristone.pdf.

[58]Citizen Petition from Am. Coll. of Obstetricians & Gynecologists to Lauren Roth, Assoc. Comm'r for Pol'y, U.S. FDA (Oct. 4, 2022), https://emaaproject.org/wp-content/uploads/2022/10/Citizen-Petition-from-the-American-College-of-Obstetrician-and-Gynecologists-et-al-10.3.22-EMAA-website.pdf.

[59]*Id.* at 12.

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121. ACOG further explained that "the Certified Provider Requirement serves no benefit to patient safety," but is instead "redundant and unnecessary."[60] Moreover, ACOG noted that the provider-certification requirement has disproportionately affected rural patients because "clinicians who have already navigated mifepristone REMS compliance to provide abortion care . . . are almost always located in cities."[61] Making matters worse, "rural residents are more likely to lack access to OBGYNs, meaning that surgical management is also less likely to be an option."[62] Moreover, "clinicians might have reasonable reservations about opting into a prescription system that could, if their certification were leaked, suggest they were an abortion provider and open them up to violence and harassment."[63]

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[60] *Id.* at 13.

[61] *Id.* at 14 (citing Bearak JM, Burke KL, Jones RK. *Disparities and change over time in distance women would need to travel to have an abortion in the USA: a spatial analysis*. Lancet Public Health. 2017; 2:e493–500 and Committee on Health Care for Underserved Women. *Health Disparities in Rural Women. American College of Obstetricians and Gynecologists.* Obstet Gynecol. 2014;123:384-388).

[62] *Id.* (citation omitted).

[63] *Id.*; *see also id.* ("Research has shown that without certification, more clinicians would prescribe mifepristone.") (citing Neill S, Goldberg AB, Janiak

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122. The ACOG's citizen petition also urged FDA not to include a pharmacy-certification requirement because "research . . . suggests that the pharmacy requirement is unnecessary to ensure that mifepristone's benefits outweigh its risks and unduly burden[s] access."[64] The petition pointed specifically to a study "conducted . . . in California and Washington state suggest[ing] that pharmacies are already equipped to dispense the drug without

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E., *Medication management of early pregnancy loss: the impact of the US Food and Drug Administration Risk Evaluation and Mitigation Strategy* [A289]. Obstet Gynecol. 2022 May;139: 83S; Calloway D, Stulberg DB, Janiak E. *Mifepristone restrictions and primary care: Breaking the cycle of stigma through a learning collaborative model in the United States.* Contraception. 2021 July; 104(1):24-28; *Mokashi M, Boulineaux C, Janiak E, Boozer M, Neill S. "There's only one use for it": stigma as a barrier to mifepristone use for early pregnancy loss in Alabama*. [A31]. Obstet Gynecol. 2022 May:139:9S-10S; and Razon N, Wulf S, Perez C, McNeil S, Maldonado L, et al. *Exploring the impact of mifepristone's risk evaluation and mitigation strategy (REMS) on the integration of medication abortion into US family medicine primary care clinics.* Contraception 2022;109(5):19-24).

[64] *Id.* at 15.

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special certification."[65] "As with the certified provider requirement," ACOG noted, "the burdens associated with the certified pharmacy requirement will also fall disproportionately on poor and rural [patients], contrary to the REMS statute."[66]

123. Finally, as ACOG pointed out, recent scholarship demonstrates that removing the REMS restrictions does not negatively affect patient safety:

> After Canada removed all restrictions on prescribing mifepristone for abortion, thereby allowing it to be prescribed and dispensed like any other drug ("normal prescribing"), there was no increase in complications from mifepristone use. [A] 2022 study . . . found no difference in the rate of any complication (0.67% vs. 0.69%) or in the rate of serious adverse events (0.03% vs. 0.04%) between the ten-month period when mifepristone was distributed with REMS-like restrictions and the twenty-eight-month period of normal prescribing after all such restrictions were lifted and mifepristone was prescribed with no special self-certification and dispensed routinely from pharmacies.[67]

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[65] *Id.* (citing Grossman D, Baba CF, Kaller S, Biggs MA, Raifman S, et al. *Medication abortion with pharmacist dispensing of mifepristone.* Obstet Gynecol 2021;137(4):613-622).

[66] *Id.* at 16.

[67] *Id.* at 17 (citing Schummers L, Darling EK, Dunn S, McGrail K, Gayowsky A, et al. *Abortion Safety and Use with Normally Prescribed Mifepristone in Canada*. N Engl J Med. 2022 Jan 6;386(1):57-67.)

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124. FDA rejected ACOG's citizen petition.[68]

125. In fact, FDA has repeatedly rejected the concerns raised by leading medical organizations and retained the medically unfounded REMS restrictions: renewing them in 2016,[69] 2019,[70] 2021,[71] and yet again in 2023.[72] FDA retained these restrictions notwithstanding its periodic reviews of the post-marketing data, which have not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days' gestation (10 weeks).[73]

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[68]U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, Letter from Patrizia Cavazzoni, M.D., Regarding Docket No. FDA-2022-P-2425, (Jan. 3, 2023), https://www.regulations.gov/document/FDA-2022-P-2425-0003, attached hereto as Ex. S.

[69]Danco Labs., LLC, Mifeprex REMS (Mar. 2016), https://www.fda.gov/media/164649/download.

[70]Danco Labs., LLC, Mifepristone REMS (Apr. 2019), https://www.fda.gov/media/164650/download.

[71]Danco Labs., LLC, Mifepristone REMS (May 2021), https://www.fda.gov/media/164651/download.

[72]Ex. L (2023 REMS).

[73]U.S. Food & Drug Admin., *Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation* (Jan. 4, 2023), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-

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126. Even as mifepristone has remained subject to the unduly burdensome REMS restrictions, a less safe mifepristone product for the treatment of Cushing's syndrome has been available for over a decade with no similar restrictions. In 2012, FDA approved Korlym (mifepristone) tablets, 300 mg, as treatment for Cushing's syndrome *without* a REMS.[74] This was done even though, as FDA noted in its 2016 Medical Review, Korlym "is taken in higher doses, in a chronic, daily fashion unlike the single 200 mg dose of Mifeprex . . . [and] the rate of adverse events with Mifeprex is much lower."[75] Patients who are prescribed Korlym take one to four pills *daily*—which is 1.5 to 6 times the recommended dose for Mifeprex.[76]

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providers/questions-and-answers-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation.

[74]HHS, Food & Drug Admin., Ctr. for Drug Evaluation & Research, *Application Number: 202107Orig1s000, Approval Letter* (Feb. 17, 2012), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202107Orig1s000Approv.pdf.

[75]Ex. B (2016 Medical Review) at 10.

[76]U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, *Application Number*: *202107Orig1s000, Labeling* (Feb. 17, 2012), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202107Orig1s000Lbl.pdf.

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127. The risks associated with mifepristone are also lower than those of many other common medications, such as Viagra, Tylenol, anticoagulants (blood thinners), and penicillin. Again, since 2000, mifepristone has been used 5.6 million times with only 28 reported associated deaths, none of which can be causally attributed to mifepristone.[77] And in nearly all cases of fatal infections associated with mifepristone, FDA has acknowledged that "the critical risk factor" is not mifepristone but "pregnancy itself," as similar infections "have been identified both in pregnant women who have undergone medical abortion and those who have not[.]"[78]

128. By contrast, as the American Academy of Family Physicians has noted, "other drugs with higher complication rates, such as acetaminophen, aspirin, loratadine, and sildenafil, do not have REMS restrictions[.]"[79]

129. Medications for erectile dysfunction have a mortality rate more than six times greater than mifepristone, and penicillin has a mortality rate three times greater than mifepristone.[80]

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[77]Ex. A (Mifepristone U.S. Post-Marketing Adverse Events Summary).

[78]Ex. F at 26.

[79]*Supra* n.52.

[80]Greer Donley, *Medication Abortion Exceptionalism*, 107 CORNELL L. REV. 627, 651–52 (2022).

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130. Likewise, acetaminophen (Tylenol) toxicity is the most common cause of liver transplantation in the U.S. and is responsible for 56,000 emergency department visits, 2,600 hospitalizations, and 500 deaths per year in the United States.[81]

131. But none of these drugs is subject to a REMS.

132. And even though opioids are highly addictive and cause tens of thousands of fatalities per year from overdoses, the opioid REMS does not require providers to do anything; it only requires that opioid manufacturers *offer* optional training to healthcare providers who prescribe opioids, who may or may not choose to take it. FDA acknowledges that "[t]here is no mandatory federal requirement that prescribers or other [health care providers] take the training and no precondition to prescribing or dispensing opioid analgesics to patients."[82]

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[81]Suneil Agrawai and Babek Khazaeni, *Acetaminophen Toxicity*, National Library of Medicine (Aug. 1, 2022), https://www.ncbi.nlm.nih.gov/books/NBK441917/#:~:text=It%20is%20responsible%20for%2056%2C000,is%20contained%20in%20combined%20products.

[82]Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS), U.S. FOOD & DRUG ADMIN. (Sept. 2018), https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems.

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133. Mifepristone use is also far safer than continuing a pregnancy. A person who carries a pregnancy to term is at least fourteen times more likely to die than a person who uses mifepristone to end a pregnancy.[83] Unequal access to adequate health care exacerbates the risk for those with less privilege. For example, Black women are three to four times more likely than white women to die a pregnancy-related death in the U.S.[84]

134. The two risks listed on the mifepristone label are also associated with many common obstetrical and gynecological procedures, such as vaginal delivery, surgical or medical miscarriage management, or insertion of an intrauterine long-acting reversible contraceptive (IUD). As the Mifeprisone Medication Guide acknowledges: "Although cramping and bleeding are an

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[83]Elizabeth G. Raymond & David E. Grimes, *The Comparative Safety of Legal Induced Abortion and Childbirth in the United States*, 119 Obstetrics & Gynecology 215, 215 (2012).

[84]Elizabeth A. Howell, MD, MPP, *Reducing Disparities in Severe Maternal Morbidity and Mortality*, 61:2 Clinical Obstetrics & Gynecology 387, 387 (2018); *see also* Claire Cain Miller, Sarah Kliff, Larry Buchanan, *Childbirth is Deadlier for Black Families Even When They're Rich, Expansive Study Finds*, N.Y. Times (Feb. 12, 2023), https://www.nytimes.com/interactive/2023/02/12/upshot/child-maternal-mortality-rich-poor.html?smid=url-share.

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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*." (Emphasis added.)[85]

G. The 2023 REMS Unduly Burdens Access to Healthcare

135. The mifepristone REMS have significantly impeded access to abortion care. And the 2023 REMS is even more unduly burdensome than prior REMS in light of dramatically restricted access to care across the United States.

136. Even before *Dobbs v. Jackson Women's Health Organization*, 142 S. Ct. 2228 (2022), only a small fraction of counties in the United States had a clinician providing surgical abortions.[86] Mifepristone offers the possibility of vastly increased access to care by enabling primary care physicians to integrate abortion care into the services they provide. But the mifepristone REMS impedes the availability of medication abortion care, and so abortion care remains beyond

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[85]Ex. R (Mifepristone Medication Guide).

[86]Na'amah Razon, Sarah Wulf, et al., *Exploring the impact of mifepristone's risk evaluation and mitigation strategy (REMS) on the integration of medication abortion into US family medicine primary care clinics*, 109 Contraception 19 (May 2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9018589/.

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the reach of many—even in states like the Plaintiff States in which abortion care is lawful and protected in various ways.[87]

137. According to one recent study, approximately 40 percent of "family physicians interviewed . . . either named or described the REMS criteria as a barrier to providing medication abortion."[88] These family physicians explained that "the REMS impede their ability to provide medication abortion within primary care" because they "require substantial involvement of clinic administration, who can be unsupportive," and because "[t]he complexity of navigating the REMS results in physicians and clinic administration . . . viewing medication abortion as not worth the effort, since it is only a small component of services offered in primary care."[89]

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[87] *Id.*

[88] *Id.*

[89] *Id.*; *see also* Sara Neill, MD, et al., *Medication Management of Early Pregnancy Loss: The Impact of the U.S. Food and Drug Administration Risk Evaluation and Mitigation Strategy* (describing a survey of obstetrician-gynecologists in which "[n]early all interviewees (17 of 19, 89%) listed the REMS as a barrier to mifepristone use. Barriers included [the] belief that the REMS indicated mifepristone was not available to general ob-gyns . . . and concerns about signing the required prescriber agreement").

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138. Another recent study of primary care physicians and administrators noted that "[a]bortion with mifepristone is safe and effective" and "falls well within the scope of primary care in the United States, as it involves patient assessment and health education for which primary care providers are extensively trained." But, the article concluded, the REMS are the "linchpin of a cycle of stigmatization that continues to keep mifepristone out of primary care practice."[90]

139. This, in turn, harms patients. Under the REMS, a person who turns to their trusted health care provider—often a family doctor or primary care physician—for a medication abortion cannot obtain that care unless the clinician is specially certified (or is willing to become specially certified), and either the clinician has arranged to stock the drug or a pharmacy serving the patient's area has also gone through the process to be specially certified. This is so even though that same provider can simply write the same patient a prescription for misoprostol, the second drug in FDA's approved regimen for medication abortion, or virtually any other prescription drug that the clinician deems medically appropriate—and a pharmacy can simply dispense it—without the need for any special certifications.

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[90]Danielle Calloway, Debra B Stulberg, & Elizabeth Janiak, *Mifepristone restrictions and primary care: Breaking the cycle of stigma through a learning collaborative model in the United States*, 104 Contraception 24 (July 2021).

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140. Forcing patients to go to "specifically certified" providers, as opposed to their primary care or family physicians, disrupts continuity of care, stigmatizes routine health care, and discourages patients from making the best healthcare choices for themselves and their families. This burden is especially harsh for patients whose access to healthcare is already diminished by poverty, language barriers, lack of transportation, racial discrimination, or other factors. And it is particularly burdensome given the limited time window in which medication abortion is available.

141. This results in worse health outcomes for patients who might otherwise rely on mifepristone to safely terminate their pregnancies, but are unable to obtain a medication abortion given the limited number of REMS-certified prescribers or pharmacies.

142. Some patients will effectively be unable to access abortion, and will carry an unwanted pregnancy to term, due to the limited number of providers who are able to prescribe mifepristone because of the REMS. A landmark study shows that patients denied abortion are more likely to: experience serious complications from the end of pregnancy, including eclampsia and death; stay tethered to abusive partners; suffer anxiety and loss of self-esteem in the short term after

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being denied abortion; and experience poor physical health for years after the pregnancy, including chronic pain and gestational hypertension.[91]

143. Still others will opt for surgical abortion, which FDA describes as a more "invasive medical procedure that increases health risks for some patients and that may be otherwise inaccessible to others."[92] As FDA acknowledges, access to mifepristone is particularly critical "[f]or patients for whom mifepristone is the medically indicated treatment because of the patient's pre-existing health condition."[93]

144. "For example," FDA has explained:

> surgical abortion involves anesthesia, but people who are allergic to anesthesia can experience a sudden drop in blood pressure with cardiorespiratory arrest, and death. And . . . patient populations for whom medication abortion is more appropriate than a surgical abortion include 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, and patients in the intensive care unit or trauma patients who have difficulty with the positioning required for suction D&C.

(Internal quotations and citations omitted.)[94]

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[91]Our Studies, *The Turnaway Study*, Advancing New Standards in Reproductive Health, https://www.ansirh.org/research/ongoing/turnaway-study.

[92]Defs.' [FDA] Opp'n to Pls.' Mot. for a Prelim. Inj., *All. for Hippocratic Med. v. FDA*, No. 2:22-cv-00223-Z (N.D. Tex. Jan. 13, 2023), ECF No. 28 at 38.

[93]*Id.* at 39.

[94]*Id.*

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145. Moreover, FDA itself has repeatedly confirmed and re-confirmed that mifepristone is safe and effective. According to FDA, mifepristone provides a "meaningful therapeutic benefit to patients" as compared to other treatments.

146. By unduly burdening patients' access to mifepristone through the 2023 REMS, FDA deprives patients of the therapeutic benefit of the drug without any scientific basis.

H. Injury to the Plaintiff States and Their Residents

Washington

147. The State of Washington's injuries exemplify those of other Plaintiff States caused by the mifepristone REMS.

148. In Washington, mifepristone is a critical medicine for providing safe and effective abortion care as well as for supporting miscarriage management.

149. In 2021 (the most recent year for which complete data is available), there were 15,358 abortions in Washington. Of those, 9,060—59%—were medication abortions using mifepristone. Fewer than 0.1% of mifepristone abortions in 2021 resulted in a complication that required hospitalization.

150. Washington providers have been hindered in providing care, and patients have been hindered in receiving care, due to the mifepristone REMS. The 2023 REMS requirements pose substantial challenges to providers and patients, and have resulted in significant expenses for state institutions, including the University of Washington (UW).

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151. The State of Washington, through the UW, its largest institution of higher education, operates UW Medicine, a group of multiple public and private nonprofit entities sharing the mission to improve the health of the public. This includes the UW's two campuses of the University of Washington Medical Center, the UW Medicine Primary Care Clinics, the UW Medical School, and through a contract with King County, Harborview Medical Center. As an owner and operator of medical facilities that provide reproductive health care services and pharmacies that dispense mifepristone, Washington is subject to and harmed by the January 2023 REMS.

152. At the UW, for instance, implementation of the 2023 REMS requirements is currently being overseen by a subcommittee of more than 20 UW physicians, administrators, and staff. To date, the subcommittee members have expended hundreds of hours on REMS implementation work, with many outstanding tasks still to complete. This is valuable time that these UW employees could otherwise spend treating patients, conducting research, or attending to other critical job functions.

153. One area in which UW has dedicated substantial resources is in its work to make the REMS-required Patient Agreement Form available to its telemedicine patients. The 2023 REMS continues to require that the Patient Agreement Form be signed by both the patient and a certified provider before a prescription can be filled by a certified pharmacy. Completing the form

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is usually a simple task in person, but it poses significant challenges in the telehealth setting. UW staff have worked more than 100 hours on both operational and technical elements to implement this REMS component, including making the Patient Agreement Form accessible to telemedicine patients in a HIPAA-compliant form and designing a method to securely transmit the form to the patient for their signature and then securely re-route the form back to the provider.

154. This work has been further complicated by the fact that some patients may not have access to or comfort with certain technologies (such as smartphones with scanning apps), making it challenging for UW to create a technology process that does not exacerbate inequities in patient access to abortion care.

155. Another area of significant time and expense has been implementation of the provider-certification requirement for telehealth providers. UW has hundreds of providers who are eligible to provide telehealth services. To ensure UW providers who may want to prescribe mifepristone are in compliance with the 2023 REMS requirements, UW is currently conducting outreach to ensure all interested, qualified providers are aware of the 2023 REMS requirements. UW operational staff then has to work with each provider who expresses an interest in prescribing mifepristone to ensure that the physician completes the Prescriber Agreement Form and transmits it to the UW Pharmacy.

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Providers then have to be trained on the new technology interfaces required for the Patient Agreement Form as well as the additional steps required in order to submit a mifepristone prescription for a medication abortion to a UW pharmacy. This outreach will likewise need to be done for UW's medical residents. This will require ongoing work as new healthcare providers and residents join UW.

156. UW has also had to devote significant time to designing electronic safeguards to help protect the safety of its providers. Some UW physicians, for instance, have expressed concern that by completing the Prescriber Agreement Form and having their name on a list of certified medication abortion prescribers, they could become a target of anti-abortion violence or harassment in the event the list were leaked or compromised.[95] Given the growing criminalization and

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[95]Abortion providers have long faced stigma, harassment, and violence. In 2021, 182 death threats were made against abortion providers. *See* National Abortion Federation, *2021 Violence & Disruption Statistics*, https://prochoice.org/wp-content/uploads/2021_NAF_VD_Stats_Final.pdf; *see also, e.g.*, U.S. Dep't of Justice, *Recent Cases on Violence Against Reproductive Health Care Providers* (Oct. 18, 2022), https://www.justice.gov/crt/recent-cases-violence-against-reproductive-health-care-providers; Megan Burbank, *Planned Parenthood awarded $110K after Spokane clinic protests*, CROSSCUT (Dec. 20, 2022), https://crosscut.com/news/2022/12/planned-parenthood-awarded-110k-after-spokane-clinic-protests]; Ted McDermott, *Windows smashed at Planned*

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penalization of abortion following the *Dobbs* decision, these concerns are further heightened for doctors who hold medical licenses in multiple states (including states where abortion laws differ from Plaintiff States') and for medical residents who later intend to practice in states where abortion is illegal or heavily restricted.[96] While UW is working hard to protect its providers—by, for example, creating additional interfaces so that a telehealth appointment for a medication

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Parenthood in Spokane Valley; suspect arrested, THE SPOKESMAN-REVIEW (July 5, 2021), https://www.spokesman.com/stories/2021/jul/05/windows-smashed-at-planned-parenthood-in-spokane-v/.

[96]Recognizing the reality of potential prosecution of Washington abortion providers, the Washington's Office of the Insurance Commissioner (OIC) recently approved coverage to reimburse physician policyholders for legal fees and expenses incurred in defending against a criminal action that comes from providing direct patient care, including abortions. As Insurance Commissioner Mike Kreidler explained, "As states like Texas threaten legal and criminal action against physicians, the OIC is determined to counter this by assisting medical malpractice insurers wherever we can." Press Release, Office of the Insurance Commissioner, New insurance coverage approved to help doctors who face criminal charges for providing legal abortions (Sept. 27, 2022), https://www.insurance.wa.gov/news/new-insurance-coverage-approved-help-doctors-who-face-criminal-charges-providing-legal.

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abortion can only be booked with a telehealth clinic (not a specific provider), thereby ensuring that an individual provider's name is not made available before the appointment—many physicians remain concerned about having to become a "certified prescriber" of medication abortion. The provider-certification requirement thus creates additional, unnecessary risks for Washington employees, providers, and residents that would not exist without the REMS. These risks have become exponentially higher in the post-*Dobbs* era, even as Washington continues to protect the right to choose and provide abortion care.

157. FDA recognizes such concerns, but disregarded them in issuing the 2023 REMS. FDA shields the identities of its own employees whose work relates to mifepristone to protect their health and safety, in light of the violence and harassment surrounding the provision of abortion.

158. The January 2023 REMS also places a significant burden on UW's pharmacies. Prior to the January 2023 REMS, UW pharmacies did not distribute mifepristone for medication abortion, as those medications had to be provided directly to the patient by the provider at an in-patient visit in a UW clinic (or, during the COVID-19 pandemic, by the provider via mail). With the easing of the in-patient and provider-only distribution requirements, UW is now working to stock mifepristone at both its inpatient pharmacies and through its mail-order pharmacy for its telehealth patients. But the requirements

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associated with becoming a certified pharmacy have created a significant additional workload for UW pharmacy team members.

159. Most significant is the requirement that UW pharmacies verify that each prescriber of mifepristone has a signed Prescriber Agreement Form on file with the pharmacy before a prescription can be filled. This has required extensive work by both UW operations and IT staff to determine how to host a dynamic list of certified providers in a secure but easily verifiable manner for UW pharmacy personnel.

160. Under the 2023 REMS program requirements, UW's pharmacies are also required to ensure that the drug is dispensed within four calendar days after the pharmacy receives the prescription (or the pharmacy must engage in additional consultation with the prescribing physician), which has required an additional workflow to ensure compliance. The same is true for the REMS requirement that authorized pharmacies record the National Drug Code (a unique identifier for drug packages) and lot number from each package of mifepristone dispensed. To date, UW pharmacy staff has expended approximately 80–100 hours on implementation work to comply with the 2023 REMS, and this work is not yet complete. The pharmacy needs additional hours to finalize these workflows and to train staff on the mifepristone REMS program requirements.

161. As demonstrated by the hundreds of hours being spent by UW physicians and staff to implement the 2023 REMS program requirements,

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compliance with the REMS program creates an expensive and substantial burden for Washington's hospitals, clinics and pharmacies. This is a financial and administrative burden that many hospitals, clinics, and pharmacies in Washington—particularly small or family-operated ones—cannot shoulder.

162. As a result, the 2023 REMS requirements unnecessarily limit the number of providers in Washington who can prescribe mifepristone and the patients' options for filling a mifepristone prescription. These unnecessary limitations, in turn, unduly burden access to mifepristone for Washington patients.

163. In eastern Washington, the student medical center at Washington State University (WSU), Cougar Health Services, has no REMS-certified providers nor is its campus pharmacy REMS-certified. WSU students seeking medication abortion cannot obtain medication abortion services at the student medical center or have a mifepristone prescription filled at the campus pharmacy, but are instead referred off-campus. This referral process is time-sensitive, requires many students to establish care at a new facility, and often creates undue stress for the student attempting to access care.

164. As the WSU example highlights, the harms caused by the REMS are particularly pronounced in central and eastern Washington, where access to abortion is already limited by a smaller density of providers and more rural population. Of the 20 eastern Washington counties, only nine have abortion

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providers. By irrationally limiting who may prescribe and dispense mifepristone, the REMS ensure that abortion care remains unavailable to many rural Washingtonians.

165. The REMS certification requirements pose particular hardships in eastern Washington for providers and pharmacies who serve patients from other states—including Idaho—or who may live in Idaho themselves. For these providers and pharmacists, putting themselves on a list of abortion providers raises serious concerns about criminal or civil liability under Idaho's draconian anti-abortion laws.

166. Moreover, the REMS pharmacy requirements also limit the number of specially certified pharmacies in Washington, thereby limiting drug availability for patients, particularly in rural communities underserved by large pharmacy chains. While mail-order prescriptions may be desirable for some, they may be infeasible or impossible for others, including patients experiencing housing insecurity; traveling from other states; close to the gestational limit; living in rural areas dependent on P.O. boxes for mail delivery—which are ineligible for mail-order prescriptions; or for whom receipt of abortion medication at home may trigger domestic violence or housing loss. For these patients, local pharmacy pick-up may be necessary—but unavailable due to the 2023 REMS requirements.

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167. For patients receiving medical care in Washington, the Patient Agreement Form creates an additional, unnecessary risk. While medical institutions and providers have enacted safeguards to ensure the safety and privacy of all medical records, the simple fact that a patient has an additional document in their medical record attesting to their medication abortion creates an added risk for patients—particularly for those patients who travel to Washington for medical treatment from states where the abortion would be illegal. Abortion providers have been targets for hackers seeking to steal information about both patients and providers. In 2021, for example, hackers accessed data about roughly 400,000 patients from Planned Parenthood Los Angeles.[97] Here in Washington, providers report frequent phishing attacks aimed at illegally obtaining information about patients and providers.

168. This risk is compounded by the fact that providers are required to provide patients with a copy of the Patient Agreement Form, which could, in turn, be found by a patient's spouse, partner, or parent (who might otherwise be unaware of the patient's medication abortion), potentially putting the patient at risk of violence or abuse. And the Patient Agreement Form is uniquely

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[97]Gregory Yee and Christian Martinez, *Hack exposes personal information of 400,000 Planned Parenthood Los Angeles patients*, LOS ANGELES TIMES (Dec. 1, 2021), https://www.latimes.com/california/story/2021-12-01/data-breach-planned-parenthood-los-angeles-patients.

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problematic for patients who receive mifepristone for miscarriage management, as they must falsely attest that they are "decid[ing] . . . to end [their] pregnancy" and then have that document placed into their medical record. And again, all of these risks are compounded for individuals traveling to Washington to receive care they cannot access in their home state.

Oregon

169. As in Washington, mifepristone is a critical medicine for providing safe and effective abortion care as well as for supporting miscarriage management in Oregon. The prescription and use of mifepristone with misoprostol is the standard of care for miscarriage management and medication abortion in Oregon.

170. According to state data for 2021, 4,246 medication abortions were administered by Oregon medical providers. Based on information available at the time of filing, it is likely that most of those medication abortions were effected with a mifepristone prescription.

171. Those 4,246 medication abortions constitute about 60 percent of abortions in Oregon in 2021. At the time of filing, the State of Oregon is not aware of any Oregon patient who has experienced serious adverse effects or death as the result of being prescribed and using mifepristone for miscarriage management or medication abortion.

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172. Oregon providers have been hindered in providing care, and patients have been hindered in receiving care, due to the mifepristone REMS. Medical providers, hospital administrators, and staff spend many hours implementing REMS requirements, including making Patient Agreement Forms available to patients and protecting the security of Provider Agreement Forms.

173. The REMS requirements also add to the amount of provider time required for each patient. Even at a conservative estimate of two to three minutes per patient, over a hundred—potentially hundreds—of provider hours are spent each year for the review, discussion, and signing of the Patient Agreement Forms. That is valuable time that those medical providers could otherwise spend treating patients or attending to other important work.

174. Those requirements are also duplicative of the counseling that Oregon providers already provide to their patients, namely in discussing risks and benefits, explaining the treatment and alternatives, and obtaining informed consent.

175. Oregon patients seeking care for miscarriage management have also experienced the same issues as similarly situated Washington patients. Namely, because the Patient Agreement Form is written specifically for the context of medication abortion, it requires them to inaccurately attest that they have decided to "end [their] pregnancy." That causes unnecessary confusion for those patients.

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176. In addition to the unnecessary (and sometimes frightening) confusion, the Patient Agreement Form has caused unwarranted additional anguish in some seeking care for miscarriage management. That is because the form does not distinguish between the use of mifepristone for miscarriage management and its use for the intentional termination of a pregnancy. Consequently, for those already dealing with the distress of losing a pregnancy, the medically unjustified REMS impose the additional emotional burden of requiring the patient to incorrectly attest that the pregnancy loss was intentional as a prerequisite for obtaining medically appropriate healthcare for their miscarriage.

177. The REMS requirements also reduce access to essential reproductive healthcare in Oregon. Namely, many rural providers in Oregon do not have the volume of patient care to justify the onerous steps required to comply with the REMS for mifepristone. As a result, rather than seek certification themselves, they often refer patients to other providers. That requires patients to see a second provider for something that their original provider otherwise could have handled quickly and safely, results in reduced patient choice, and also places the burden of additional patient loads on those certified providers that accept referrals.

178. And similar to Washington patients, the reduced access to essential reproductive health care results in additional delays to patients receiving

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healthcare. For example, it takes time for the patient to receive the referral from their primary provider. It takes time for the patient to establish care with the second provider. It can take additional time if the patient seeks in-person consultation and needs to travel for care. And it takes time for the patient to wait for any healthcare delays caused by the patient-load resulting from the number of referrals. Those are delays to healthcare for conditions for which time is of the essence. And those delays often contribute to patients having reduced availability of healthcare options and adverse effects to patient health.

Arizona

179. Access to safe and effective medication abortion is critically important for Arizonans. Arizonans experience harms as a result of the 2023 REMS that are similar to those experienced by residents of the Plaintiff States.

Colorado

180. The State of Colorado, through the University of Colorado, its largest institution of higher education, operates a woman's health clinic. As an owner and operator of a medical clinic that provides reproductive health care services and dispenses mifepristone, Colorado is subject to and harmed by the January 2023 REMS.

181. Providers and staff at the University of Colorado have expended time and resources complying with the 2023 REMS requirement, including developing and processing the Prescriber Agreement Form and the

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Patient Agreement Form. Further, the 2023 REMS prevent non-certified providers from prescribing mifepristone to their patients. As a result, those patients often must make additional clinic visits—sometimes at different locations—to obtain mifepristone.

182. Further, patients in Colorado suffer the same harms experienced by patients in other states outlined above and below.

Connecticut

183. Access to safe and effective medication abortion is critically important for Connecticut residents. Connecticut residents experience harms as a result of the 2023 REMS that are similar to those experienced by residents of the Plaintiff States.

Delaware

184. Like Washington, Delaware residents rely on mifepristone to access safe and effective abortion care and management of miscarriages. Analysis of data from 2014 to 2020 shows that Delawareans have increasingly relied on medication abortion for early pregnancy termination. In 2014, there were 2,937 abortions in Delaware. Of those, 1,292—44%—were medical abortions using mifepristone. In 2020 (the most recent year for which complete data is available), there were 2,281 abortions in Delaware. Of those, 1,492—65.4%—were medical abortions using mifepristone.

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185. Restricting access to mifepristone needlessly harms Delawareans who increasingly rely on it.

Illinois

186. In Illinois, mifepristone is a critical medicine for providing safe and effective abortion care as well as for supporting miscarriage management.

187. In 2020 (the most recent year for with public data), there were 46,243 reported abortions in Illinois. Of those, 23,765—51%—were medication abortions using mifepristone.

188. The mifepristone REMS requirements impede drug availability for Illinois residents by limiting the providers that can prescribe and the pharmacies that can dispense the medication, while creating additional barriers to patient access through the Patient Agreement Form requirement.

189. Limited access to abortion and miscarriage management medication increases other health care costs, including more expensive procedural or later-stage abortion care, emergency care, and care related to complications due to unwanted pregnancies, childbirth, and miscarriage.

190. A significant proportion of this cost is borne by the State, which is one of only 16 states that goes beyond federal Medicaid limits and uses state funds to cover abortion care for people enrolled in Medicaid. From January 2019 to May 2022, the State covered approximately 29,000 mifepristone prescriptions.

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191. State Medicaid reimbursement rates are higher for procedural abortions and abortions taking place later in gestation. The bundled State Medicaid reimbursement rate for medication abortion is $558. In contrast, the lowest rate for a procedural abortion is $798. Because the 2023 REMS requirements artificially limit the number of providers who can prescribe mifepristone and the pharmacies that can fill prescriptions, fewer people have access to mifepristone abortions. This restriction results in more higher-cost procedural abortions. Broad mifepristone access is a critical tool for addressing the financial impact on the State.

192. As Illinois's neighboring states have curtailed abortion access, Illinois has seen a 28% increase in abortions from April 2022 to August 2022, creating additional strain on Illinois providers and healthcare systems. The REMS certification requirements pose particular hardships for Illinois providers and pharmacies because Illinois is an abortion oasis in the Midwest and a significant portion of patients seeking abortion care in Illinois are traveling from Indiana, Missouri, and other nearby states where abortion is restricted. For these providers and pharmacists, as well as patients traveling from out of state, the REMS certification requirements and Patient Agreement Form create additional risks of civil or criminal liability.

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Attorney General of Michigan

193. Access to safe and effective medication abortion is critically important for Michiganders. Michiganders experience harms as a result of the 2023 REMS that are similar to those experienced by residents of the Plaintiff States.

Nevada

194. In Nevada, mifepristone is widely used in combination with misoprostol as a safe, effective, FDA-approved regimen for medication abortions. It is also used in the medical management of early pregnancy loss.

195. Medication abortions represent the largest share of pregnancy termination procedures performed in Nevada. From December 2021 to November 2022, 49% of all abortions performed in Nevada were medication abortions.

196. The Nevada Department of Health and Human Services, Division of Health Care Financing and Policy (DHHS) administers the Medicaid program in Nevada. It is responsible for ensuring high quality, cost-effective care to Medicaid recipients while maintaining compliance with federal Medicaid requirements.

197. Nevada Medicaid fee-for-service covers mifepristone.

198. The reduced availability of mifepristone will financially impact DHHS. Providers and patients will be forced to adopt alternatives including

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surgical abortions which are more invasive, costly, and can expose patients to higher health risks, e.g., excessive bleeding.

199. Since the *Dobbs* decision, Nevada has experienced a marked increase in out-of-state patients seeking abortion care in state. In 2021, Nevada experienced an average of 47 out-of-state patients per month over a six-month period. In the first half of 2022, the average increased to 55 out-of-state patients. Post-*Dobbs*, there was an immediate spike of 113 in July 2022, after which the average leveled to 80 out-of-state patients per month.

200. The reduced availability of mifepristone will financially burden Nevada reproductive healthcare providers attempting to service this increased patient load.

201. The Mifepristone REMS program imposes medically unnecessary barriers to the prescription, distribution, and use of mifepristone by Nevada clinicians and patients. The REMS Patient Agreement Form must be signed by both a patient and a certified provider before a prescription can be filled by a qualified pharmacy. This imposes a significant burden for telehealth patients or patients without access to smartphones or scanning apps.

202. A pharmacy can only become qualified by undergoing the REMS certification process which further limits the availability of mifepristone in Nevada.

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203. The barriers created by the REMS program disproportionately burden people of color, low-income families, and communities within Nevada's large rural regions whose residents would have to travel long distances to seek alternative reproductive healthcare services.

204. These barriers interfere with Nevada's inherent authority to provide for the health and welfare of its residents.

New Mexico

205. New Mexico's injuries are exemplified in the sections discussing Washington's and the other Plaintiff States' injuries.

206. New Mexico repealed its antiquated prohibition of abortion in 2021.[98]

207. Nonetheless, many communities in New Mexico—particularly the rural communities—do not currently have adequate access to reproductive health care services.

208. New Mexico's injuries are exacerbated by various local cities and counties in the State of New Mexico enacting ordinances attempting to regulate abortion, declaring unlawful the delivery of abortion medications, and creating a private cause of action against abortion clinics. New Mexico residents in these cities and counties, as well as in other rural communities in the State, are particularly subject to the harms described in this Complaint.

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[98]NMSA 1978, §§ 30-5-1 to -3 (repealed 2021).

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Rhode Island

209. In Rhode Island, mifepristone is a critical medicine for providing safe and effective abortion care as well as for supporting miscarriage management.

210. The mifepristone REMS requirements impede drug availability for Rhode Islanders by limiting the providers that can prescribe and the pharmacies that can dispense the medication, while creating additional barriers to patient access through the Patient Agreement Form requirement.

211. Limited access to abortion and miscarriage management medication increases other health care utilization costs, including emergency care, resulting from complications due to unwanted pregnancies, childbirth, and miscarriage. A significant proportion of this cost is borne by the state, in which over 30% of Rhode Islanders are enrolled in Medicaid.

212. Rhode Islanders are harmed when access to mifepristone is limited, including the emotional, financial, and social harms that individuals experience by having to carry an unwanted pregnancy to term or not having access to the benefit of miscarriage management medication.

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Vermont

213. Medication abortion is critically important for Vermonters. In 2019, 59% of abortions in Vermont were medication abortions; in 2020, that number rose to 75%.[99]

214. The harms that the REMS cause are particularly acute in Vermont because the state's rurality makes it difficult for many Vermonters to access providers. Less than a third of Vermont counties have abortion providers—meaning that 43% of women of reproductive age live in a county without an abortion provider.[100]

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[99]Agency of Human Services, *Vermont 2019 Vital Statistics: 135th Report Relating to the Registry and Return of Births, Deaths, Marriages, Divorces, and Dissolutions* at 139, Vermont Department of Health (June 2021), https://www.healthvermont.gov/sites/default/files/documents/pdf/HS-VR-2019VSB_final.pdf; Agency of Human Services, *Vermont 2020 Vital Statistics: 136th Report Relating to the Registry and Return of Births, Deaths, Marriages, Divorces, and Dissolutions* at 142, Vermont Department of Health (July 2022) https://www.healthvermont.gov/sites/default/files/documents/pdf/Vital%20Statistics%20Bulletin%202020.pdf.

[100]Jesse Philbin, et al., *10 US States Would Be Hit Especially Hard by a Nationwide Ban on Medication Abortion Using Mifepristone*, GUTTMACHER

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V. FIRST CAUSE OF ACTION
(Administrative Procedure Act—Agency Action in Excess of Statutory Authority and Contrary to Law)

215. The Plaintiff States reallege and incorporate by reference the allegations set forth in each of the preceding paragraphs of this Complaint.

216. FDA's promulgation of the mifepristone 2023 REMS was a final agency action that is causing the Plaintiff States irreparable harm for which the States have no other adequate remedy under 5 U.S.C. § 704.

217. This Court must "hold unlawful and set aside agency action" that is, *inter alia*, "not in accordance with law," "in excess of statutory jurisdiction, authority, or limitations," or "without observance of procedure required by law[.]" 5 U.S.C. § 706(2).

218. Through their actions described above, Defendants violated 5 U.S.C. § 706(2)(C) by acting in excess of statutory jurisdiction, authority, limitations, and short of statutory right in promulgating the mifepristone 2023 REMS.

INSTITUTE (Feb. 7, 2023), https://www.guttmacher.org/2023/02/10-us-states-would-be-hit-especially-hard-nationwide-ban-medication-abortion-using.

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VI. SECOND CAUSE OF ACTION
(Administrative Procedure Act—Arbitrary and Capricious Agency Action)

219. The Plaintiff States reallege and incorporate by reference the allegations set forth in each of the preceding paragraphs of this Complaint.

220. FDA's promulgation of the mifepristone 2023 REMS was a final agency action that is causing the Plaintiff States irreparable harm for which the States have no other adequate remedy under 5 U.S.C. § 704.

221. FDA's promulgation of the mifepristone 2023 REMS was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

VII. THIRD CAUSE OF ACTION
(Administrative Procedure Act—Action Contrary to Constitutional Right)

222. The Plaintiff States reallege and incorporate by reference the allegations set forth in each of the preceding paragraphs of this Complaint.

223. FDA's promulgation of the mifepristone 2023 REMS was a final agency action that is causing the Plaintiff States irreparable harm for which the States have no other adequate remedy under 5 U.S.C. § 704.

224. FDA's promulgation of the mifepristone 2023 REMS treated similarly situated parties differently without adequate justification, and therefore violates the constitutional guarantee of equal protection in violation of 5 U.S.C. § 706(2)(B).

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VIII. FOURTH CAUSE OF ACTION
(Equal Protection)

225. The Plaintiff States reallege and incorporate by reference the allegations set forth in each of the preceding paragraphs of this Complaint.

226. Through their actions described above, Defendants violate the equal protection guarantee of the Due Process Clause of the Fifth Amendment to the United States Constitution.

227. Through the 2023 REMS, FDA reduces access to a critical and time-sensitive health care service needed by pregnant people. And FDA treats providers, pharmacists, and patients who prescribe, dispense, or use mifepristone worse than providers, pharmacists, and patients who prescribe, dispense, or use nearly every other medication. FDA's actions are irrational and violate the Fifth Amendment under any standard of review.

IX. PRAYER FOR RELIEF

WHEREFORE, Washington, Oregon, Arizona, Colorado, Connecticut, Delaware, Illinois, Attorney General of Michigan, Nevada, New Mexico, Rhode Island, and Vermont pray that the Court:

a. Declare, pursuant to 28 U.S.C. § 2201, that mifepristone is safe and effective and that Defendants' approval of mifepristone is lawful and valid;

b. Declare, pursuant to 28 U.S.C. § 2201, that the mifepristone REMS violates the Administrative Procedure Act;

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c. Declare, pursuant to 28 U.S.C. § 2201, that the mifepristone REMS violates the United States Constitution;

d. Enjoin Defendants, pursuant to 28 U.S.C. § 2202, from enforcing or applying the mifepristone REMS;

e. Enjoin Defendants, pursuant to 28 U.S.C. § 2202, from taking any action to remove mifepristone from the market or reduce its availability; and

f. Award such additional relief as the interests of justice may require.

DATED this 23rd day of February 2023.

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Table of Contents
Complaint Exhibits

Exhibit	Document
O	Mifepristone Prescriber Agreement Forms
P	Mifepristone Pharmacy Agreement Forms
Q	Mifepristone Patient Agreement Form
R	Mifepristone Medication Guide
S	U.S. Food & Drug Admin., Center for Drug Evaluation & Research, Letter from Patrizia Cavazzoni, M.D., Regarding Docket No. FDA-2022-P-2425, Jan. 3, 2023

Exhibit A

TTT # 2022-2468
NDA 020687
ANDA 091178
Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2022

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 2022 is approximately 5.6 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[†] - 06/30/22
Died [‡]	28
*Ectopic pregnancies [||]	97

[†] U.S. approval date

[‡] The fatal cases are included regardless of causal attribution to mifepristone. Deaths were associated with sepsis in nine of the 28 reported fatalities (eight cases tested positive for *Clostridium sordellii*, and one case tested positive for *Clostridium perfringens*). Eight of the nine fatal sepsis cases reported vaginal misoprostol use; one case reported buccal misoprostol use. Eighteen of the 19 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; probable anaphylactic medication reaction; and a case of natural death due to severe pulmonary emphysema. In the nineteenth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. There were 13 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); sepsis (*Enterococcus faecalis* and *Escherichia coli* were identified in blood culture); 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 - 06/30/22[‡]
Cases with any adverse event	2740	1473
Hospitalized, excluding deaths	768	280
*Experienced blood loss requiring transfusions [§]	416	188
Infections [‖] (*Severe infections [¶])	308 (57)	106 (14)

[†] 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.

Exhibit B

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
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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:

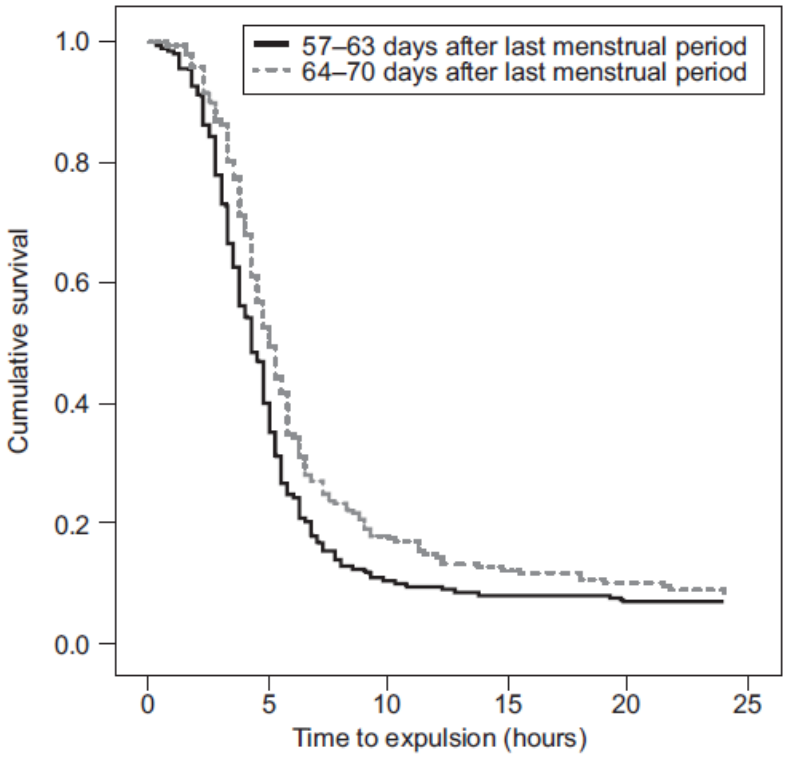
The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol should be approved for use through 70 days gestation (10 weeks from the first day of the LMP).

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).

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[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.

APPEARS THIS WAY ON ORIGINAL

[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

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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

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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)

Reviewing Medical Officers — Date: 7/16/15

(b) (6)

Date: 7/16/15

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)

07/16/2015

(b) (6)

07/17/2015

(b) (6)

07/17/2015

Exhibit C

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/default.htm)

Approved Risk Evaluation and Mitigation Strategies (REMS)

REMS Reports

Please note: The data for active/inactive status in the historical download file is not accurate. We are working on a fix for the data and will update the site when the issue is resolved.

- **REMS count**
  Currently, there are 61 REMS.
  - 57 [93%] include "elements to assure safe use' (ETASU). REMS with ETASU typically require clinicians or health care settings to become certified prior to prescribing and to participate in additional REMS activities, such as training, patient counseling, and monitoring.
  - 2 [3%] include only a "communication plan" REMS element which is informational in nature. These communication plans are typically composed of letters, websites, and fact sheets describing the specific safety risks identified in the REMS.
  - 1 [2%] include only the "medication guide" REMS element. Even products that do not have "medication guide" REMS elements may have medication guides as part of their labeling.
  - 1 [2%] include the "communication plan" AND "medication guide" REMS elements only.
- **Released REMS (/scripts/cder/rems/index.cfm?event=csvReleasedReportRems.page)**
  This report lists information for released REMS (products whose REMS program is no longer in effect) including the date the REMS was approved, date the REMS was released, and if the REMS is a shared system.

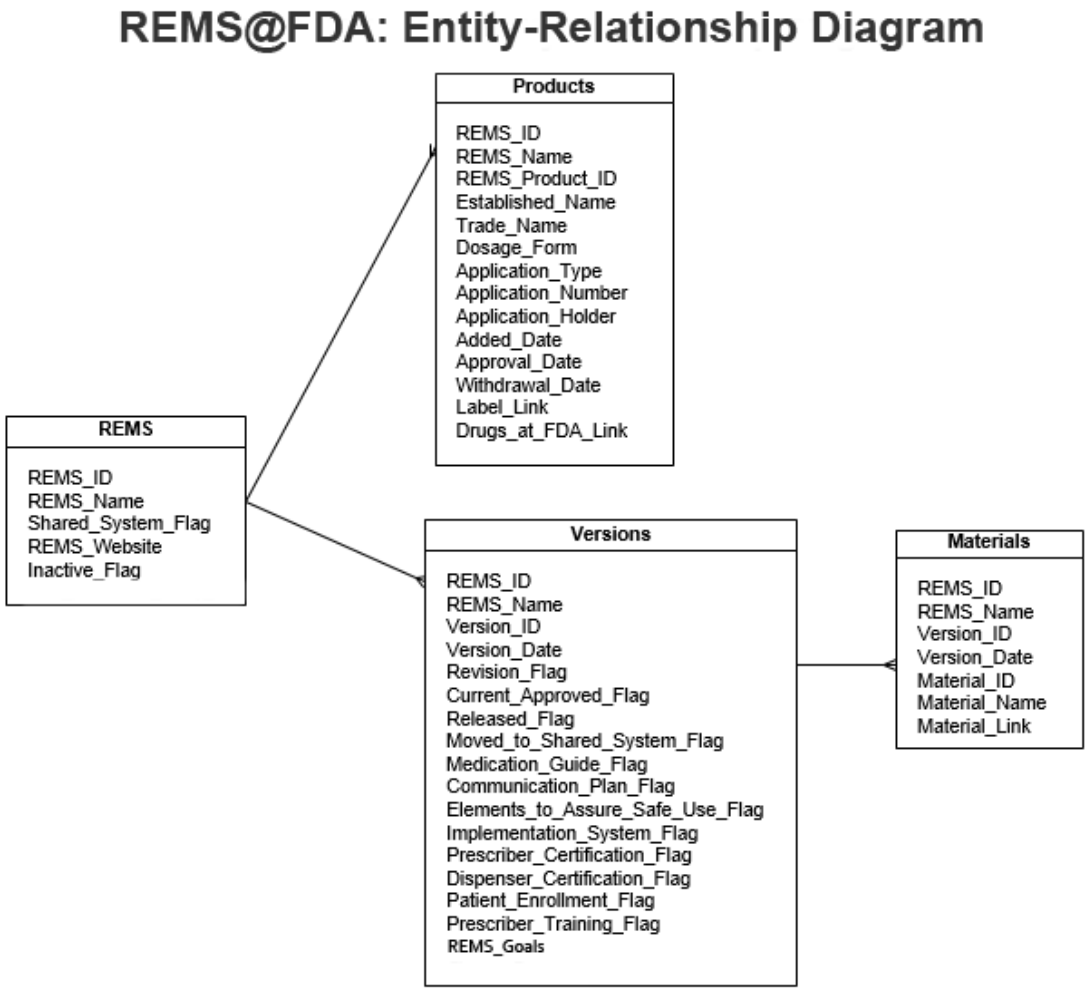
REMS Data Files and Historic REMS Information

The information presented on this website, as well as historic information about REMS and their modifications, is compiled in the REMS Data Files below. All files below include information about current REMS as well as REMS that are no longer in place.

- **Download REMS data (Includes Released REMS) (REMS.csv) (/scripts/cder/rems/index.cfm?event=csvAllRems.page)**
  This file presents a list of all approved REMS, including REMS that are no longer in place.
- **Download REMS Versions data (REMS_Versions.csv) (/scripts/cder/rems/index.cfm?event=csvModification.page)**
  This file includes details on all modifications and revisions to each REMS program, including information on no-longer-current revisions and modifications.
- **Download REMS Products data (REMS_Products.csv) (/scripts/cder/rems/index.cfm?event=csvRemsProduct.page)**
  This file includes data on all of the drugs that have ever been part of a REMS program, including information on products that are no longer marketed and/or no longer subject to a REMS.
- **Download REMS Materials data (REMS_Materials.csv) (/scripts/cder/rems/index.cfm?event=csvMaterials.page)**
  This file includes a list of all materials that have been a part of the REMS, and provides links to REMS materials stored at FDA's website, when available. This includes materials that are no longer part of a current REMS.

Data Description

The data available on this page is organized into four tables, each of which can be viewed on its own or in combination with other tables as part of a relational database. The entity-relationship diagram below shows the fields in each of these tables and how they should be linked together to form a comprehensive REMS database:



The following is a description of each table and its data:

1. **REMS**
   The **REMS** table includes one record for each REMS program, including REMS that are no longer in place. Detailed information about each REMS program is not included in this table, but can be found in the REMS Versions table.
   This table includes the following fields:
   - **REMSID**: A unique key used to identify each REMS.
   - **REMS_Name**: The name used on the REMS website to refer to the REMS program. Generally, single-product REMS are referred to by the brand name of the product, while shared system REMS are referred to by the name of the molecule or class to which they apply.
   - **Shared_System_Flag**: A flag that indicates whether a REMS is a shared system REMS.
   - **REMS_Website**: A link to the application-holder's official website for the REMS.
   - **Inactive_Flag**: A flag that indicates REMS programs that are no longer active. A REMS program may become inactive if the REMS requirement is released, if it is a single-product REMS that is incorporated

into a shared system, or if all products under the REMS have been withdrawn and are published in the Federal Register (FR).

2. **Versions**
   The REMS **Versions** table includes a record for each change to the REMS, including a record for each newly approved REMS, an additional record for each modification or revision to that REMS, and a record when the REMS requirement is released or the REMS is moved to a shared system. For more information about REMS revisions and modifications, please see FDA's Draft Guidance, **Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM441226.pdf)**.
   This table includes the following fields.
   - **REMSID**: A unique key used to identify each REMS.
   - **REMS_Name**: The name used on the REMS website to refer to the REMS program. Generally, single-product REMS are referred to by the brand name of the product, while shared system REMS are referred to by the name of the molecule or class to which they apply.
   - **VersionID**: A unique key used to identify the version of the REMS.
   - **Version_Date**: The date this version of the REMS was approved. The earliest version_date of the REMS is the date that the REMS was initially approved. For REMS that are no longer in place, the latest version_date indicates the date that the REMS was removed.
   - **Revision_Flag**: A flag that indicates whether this version of the REMS is a revision as defined in FDA's Draft Guidance, Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry. REMS revisions are defined as being limited to editorial changes, corrections of typographical errors, and changes in the application holder name or address. If the flag is equal to 0, this indicates that this version of the REMS is a newly approved REMS or a modification to that REMS.
   - **Current_Approved_Flag**: A flag that indicates whether this is the most recent version of a currently approved REMS (i.e., the version of the REMS that would appear on the REMS website homepage).
   - **Released_Flag**: A flag that indicates whether the REMS was released as of that version_date.
   - **Moved_to_Shared_System_Flag**: A flag that indicates whether the REMS was moved to a shared system as of that version_date.
   - **Medication_Guide_Flag**: A flag that indicates whether a REMS has a Medication Guide as one of its elements. Note that many REMS products have medication guides that are not part of the REMS program and are not captured here. For a full list of medication guides, click here.
   - **Communication_Plan_Flag**: A flag that indicates whether this version of the REMS has a communication plan as one of its elements.
   - **Elements_to_Assure_Safe_Use_Flag**: A flag that indicates whether this version of the REMS has elements to assure safe use.
   - **Implementation_System_Flag**: A flag that indicates whether this version of the REMS has an implementation system as one of its elements. This applies only to REMS with elements to assure safe use.
   - **Prescriber_Certification_Flag**: A flag that indicates whether this version of the REMS requires prescribers to become certified in order to be able to prescribe the drug. This applies only to REMS with elements to assure safe use.
   - **Dispenser_Certification_Flag**: A flag that indicates whether this version of the REMS requires dispenser to become certified in order to be able to dispense the drug. This applies only to REMS with elements to assure safe use.
   - **Patient_Enrollment_Flag**: A flag that indicates whether this version of the REMS requires patients to be enrolled in the REMS program. This applies only to REMS with elements to assure safe use.
   - **Prescriber_Training_Flag**: A flag that indicates whether the REMS provides training to prescriber as part of its Elements to Assure Safe Use.
   - **REMS_Goals**: The goals for each REMS Program, as specified in the REMS Document.
3. **Products**
   The **Products** table includes a record for each application that has been subject to a REMS.
   This table includes the following fields
   - **REMSID**: A unique key used to identify each REMS.

- **REMS_Name**: The name used on the REMS website to refer to the REMS program. Generally, single-product REMS are referred to by the brand name of the product, while shared system REMS are referred to by the name of the molecule or class to which they apply.
- **ProductID**: A unique key used to identify the drug
- **Established_Name**: The official nonproprietary name assigned to the drug. Generally, this is the "generic" name of the drug.
- **Trade_Name**: The proprietary or brand name for the drug, where it exists. Many generic products do not have trade names.
- **Dosage_Form**: The dosage form of the drug.
- **Application_Type**: The type of marketing approval the drug received. A drug may be marketed under a New Drug Application (NDA), Biologics License Application (BLA), or as a generic drug under an Abbreviated New Drug Application (ANDA).
- **Application_Number**: The number assigned by FDA staff to each application. One drug can have more than one application number if it has different dosage forms or routes of administration.
- **Added_Date**: The date the drug was added to the REMS. For most drugs, this is the same as the date that the REMS was initially put into place, but the dates may be different, if, for instance, a new drug is added to an existing shared system.
- **Approval_Date**: The date the drug was initially approved for marketing.
- **Withdrawal_Date**: The date published in the Federal Register announcing the drug was withdrawn from the market. If the drug was not withdrawn or the withdrawal was not announced in the Federal Register then this date will be blank.
- **Label_Link**: A link to the drug's label on DailyMed. DailyMed is a website hosted by the National Library of Medicine that provides information on the drug's current labeling. The current labeling shown on DailyMed may be different from the version that was initially approved by FDA and displayed at Drugs@FDA.
- **Drugs_at_FDA_Link**: A link to regulatory information about a drug at Drugs@FDA. Drugs@FDA is a catalog that provides information about FDA-approved products, including the product's approval history, FDA-approved labeling, therapeutically equivalent products, and consumer information.

4. **Materials**
   The **Materials** table includes a record for each material included as part of each version of the REMS. As used in this database, the term REMS materials refers to both the REMS document and the REMS' appended materials designed for stakeholders. Most information about REMS materials is available only for REMS versions that were current as of July 31, 2014 or later.
   This table includes the following fields:
   - **REMSID**: A unique key used to identify each REMS
   - **REMS_Name**: The name used on the REMS website to refer to the REMS program. Generally, single-product REMS are referred to by the brand name of the product, while shared system REMS are referred to by the name of the molecule or class to which they apply.
   - **MaterialID**: A unique key used to identify the REMS material
   - **Material_Name**: The name of the material, as specified in the REMS document
   - **Material_Link**: A link to download the material from the REMS website.
   - **VersionID**: A unique key used to identify the version of the REMS
   - **Version_Date**: The date this version of the REMS was approved. The earliest version_date of the REMS is the date that the REMS was initially approved. For REMS that are no longer in place, the latest version_date indicates the date that the REMS was removed.

*Many products within these REMS programs have Medication Guides not part of the REMS program. For a full list of Medication Guides **click here (http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm)**.

Exhibit D

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: [redacted] /S/ SEP 28 2000

SUBJECT: [redacted] Memo

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.

APPEARS THIS WAY
ON ORIGINAL

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.

APPEARS THIS WAY
ON ORIGINAL

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 Exelgyn Laboratories 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 Exelgyn 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 Exelgyn's 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.

APPEARS THIS WAY
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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.

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Exhibit E

United States Government Accountability Office

GAO

Report to Congressional Requesters

August 2008

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex

GAO-08-751

August 2008

GAO Accountability · Integrity · Reliability

Highlights

Highlights of GAO-08-751, a report to congressional requesters

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex

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 (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)
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

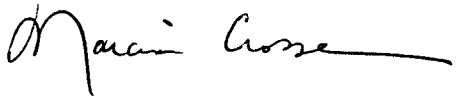
patients using the drug. The sponsor added a boxed warning about potential liver injury to the labeling and issued a letter to health care providers to alert them to the potential risk. In general, the actions FDA took in response to safety concerns were similar across all of the drugs.

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.

Appendix III: Prescriber's Agreement for Mifeprex Distribution

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

Appendix III: Prescriber's Agreement for Mifeprex Distribution

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
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

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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Exhibit F

DEPARTMENT OF HEALTH & HUMAN SERVICES

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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

[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 "presenee 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 ≤ 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.

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.

Exhibit G

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

(b) (6)

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	October 10, 2013
Drug Name(s):	Mifeprex (mifepristone) 200 mg tablets
Therapeutic Class:	progesterone-receptor modulator
Dosage and Route:	Mifepristone 600 mg as a single oral dose followed by misoprostol 400 micrograms on Day 3
Application Type/Number:	NDA 020687/Danco Laboratories
(b) (6) #:	(b) (4) 2012-1287

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CONTENTS

EXECUTIVE SUMMARY

This review evaluates if the risk evaluation and mitigation strategy (REMS) for Mifeprex (mifepristone 200 mg tablets) continues to be necessary to ensure the benefits of the product outweigh its risks.

Mifeprex was approved on September 28, 2000 with a restricted distribution program requiring prescribers attest that they are knowledgeable about the safe and appropriate use of Mifeprex. The program was approved as a REMS on June 8, 2011. The goals of the REMS are:

- To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
- 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.

Since the approval of Mifeprex, safety concerns have been reported by certified prescribers, including serious infection and hemorrhage sometimes leading to the need for transfusions, hospitalization, and death. We reviewed the current Mifeprex safety data and researched what factors may affect its safe use for patients. Our key findings include that:

- The overall safety profile of Mifeprex has not changed over the last 6-7 years and is consistent with current product labeling.
- There have been a small number of serious complications associated with Mifeprex reported and this is likely reflective of the use of Mifeprex within a system of knowledgeable healthcare providers, safe use protocols, and proper patient counseling.
    - Planned Parenthood and other family planning clinics account for the majority of Mifeprex use. Planned Parenthood implements the REMS requirements (b) (4).

Accurate gestation dating, patient education, dispensing Mifeprex directly to the patient during the office visit, and timely access to medical care remain important components to ensure the safe use of Mifeprex in order to maintain the current safety profile. Medical abortion accounts for the minority of abortions in the U.S. Similarly, training opportunities in medical abortion appear limited and are less available than surgical abortion experience. Given this relative lack of familiarity and experience with medical abortion, a restricted distribution program that reinforces the necessary skills and appropriate care (i.e., counseling and follow-up) is necessary to assuring safe use of Mifeprex. It is not likely that the essential safe use conditions will be maintained to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events. For these reasons, we believe the Mifeprex REMS provides the foundation to ensure the implementation of these safe use conditions with Mifeprex use.

(b) (6) therefore recommends that the existing elements of the REMS be maintained. Specifically, prescriber certification and dispensing limited to certain healthcare settings provide a framework to ensure that the benefits of Mifeprex outweigh its risks in an appropriate patient population.

INTRODUCTION

This review evaluates if the risk evaluation and mitigation strategy (REMS) continues to be necessary to ensure the benefits outweigh the risks for Mifeprex (mifepristone 200 mg tablets).

(b) (4)

During a (b) (6) meeting on October 4, 2012[2], the Center Director requested that the REMS for Mifeprex be re-evaluated to determine if a REMS continues to be necessary to ensure that the benefits outweigh the risks, (b) (4)

The merits of (b) (4) for mifepristone 200 mg is addressed in a separate memorandum.

1 BACKGROUND & REGULATORY HISTORY OF MIFEPREX REMS

On September 28, 2000, Mifeprex was approved for the medical termination of intrauterine pregnancy through 49 days' gestation under 21 CFR 314.520 Subpart H.[3] According to the September 28, 2000 (b) (6) review, "the success of medical termination of pregnancy decreased with advancing gestational age and incidence of adverse events increased with advancing gestational age." In addition, the review states that timely access to medical care to manage serious complications is necessary. The (b) (6), 's approval memo states, "[t]he 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 pregnancies (and other requirements), goals of safe and appropriate use may be achieved."[4]

As a result, FDA concluded Mifeprex must be available only through a restricted distribution program and required the program under Subpart H.

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1 (b) (4) (b) (4)

2 (b) (4), (b) (6)

3 Mifeprex Approval Letter signed September 28, 2000.

4 (b) (6) (b) (6) Memo. Signed September 28, 2000.

In 2007, Congress amended the FD&C Act to give FDA the authority to require a REMS when necessary to ensure that the benefits of a drug outweigh its risks.[5] Mifeprex was included on the list of products deemed to have in effect an approved REMS.[6]

The Mifeprex restricted distribution program was approved as a REMS on June 8, 2011 and contains the following elements:[7, 8]

A. Goals

- To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
- 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.

B. Medication Guide

C. Elements to Assure Safe Use, including:

a. Healthcare providers who prescribe Mifeprex will be specially certified by agreeing or attesting to the conditions set forth in the Prescriber Agreement.

b. Mifeprex will be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals.

c. Mifeprex will only be dispensed to patients with documentation of safe use conditions.

D. An Implementation System that requires Danco to:

a. Certify distributors. To become certified, distributors must agree to:

i. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.

ii. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.

b. Assess the performance of the certified distributors with regard to the following:

i. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.

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[5] Food and Drug Administration Amendments Act (FDAAA) of 2007, Pub. L. No. 110-85, Title IX, Subtitle A, Section 901, 121 Stat. 823 (2007).

[6] See Identification of Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies (REMS) for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16313 (Mar. 27, 2008).

[7] Memorandum of meeting minutes for April 28, 2011 meeting between Danco and FDA. Signed by (b) (6) on June 3, 2011.

[8] Mifeprex REMS Approval Letter. Signed by (b) (6) on June 8, 2011.

ii. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.

c. If Danco determines the distributors are not complying with these requirements, Danco will take steps to improve their compliance.

E. A Timetable for Submission of Assessments that requires Danco to submit REMS assessments to FDA one year from the date of approval of the REMS and every three years after.

The next REMS assessment is due June 2015.

2 SAFETY PROFILE OF MIFEPREX

2.1 BACKGROUND

Abortion is one of the most common procedures undergone by women of reproductive age in the United States.[9] Since 1969, the Centers for Disease Control and Prevention (CDC) has conducted abortion surveillance to document the number and characteristics of women obtaining legal, induced abortions. The 2009 data is the most recent year available. The CDC requests data from 52 reporting areas (i.e., 50 states, District of Columbia, and New York City). The areas provide information voluntarily; 45 areas reported data every year from 2000 – 2009. In most states, collection of abortion data is facilitated by the legal requirements for hospitals, facilities, and physicians to report abortions to a central health agency. These health agencies in turn voluntarily provide aggregate data to the CDC. For medical abortions, the CDC abortion surveillance summary does not include specific information on what medications and dosages are used.

A total of 784,507 abortions were reported to the CDC for 2009. Approximately 17% (16.2% ≤ 8 weeks' gestation, 0.9% >8 weeks' gestation) of abortions were reported as medical.[10,11] This is a slight increase from 2008 data (14.1% ≤ 8 weeks' gestation, 0.7% >8 weeks' gestation).[12]

In 2009, most (64.0%) abortions were performed at ≤8 weeks' gestation, and 91.7% were performed at ≤13 weeks' gestation. Among areas that reported data every year during 2000 – 2009, the percentage of abortions performed at ≤ 8 weeks' gestation increased 12% from 2008 to 2009.

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[9] Jones K et al. Abortion in the United States: Incidence and access to services, 2005. Perspect Sex Reprod Health 2008;41(1): 6-16.

[10] "the administration of medication or medications to include an abortion; at ≤8 weeks' gestation, typically involves the use of mifepristone and misoprostol; at >8 weeks' gestation, typically involves the use of vaginal prostaglandins". CDC does not report on specific medications and dosages used.

[11] Pazol K et al. Abortion Surveillance – United States, 2009. MMWR Surveillance Summaries 2012;61:1-44. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6108a1_htm?s_cid=ss6108a1_w#Tab24.

[12] Pazol K et al. Abortion Surveillance – United States, 2008. MMWR Surveillance Summaries 2011;60:1-40. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6015a1_htm?s_cid=ss6015a1_w.

2.2 SERIOUS COMPLICATIONS ASSESSED THROUGH THE REMS

Serious complications[13] assessed through the Mifeprex REMS include:

1. Hospitalizations
2. Transfusions of 2 or more units of packed cells or whole blood or having a hemoglobin of 6 gm/dL or less or a hematocrit of 18% or less
3. Serious infection, sepsis
4. Death
5. Other serious and unexpected adverse events

As of October 31, 2012, approximately 1.88 million women in the U.S. have been treated with Mifeprex for termination of pregnancy with 2,740 adverse events reported cumulatively (14 deaths, 768 hospitalizations, 66 ectopic pregnancies, 416 reports of blood loss requiring transfusion, and 308 infections [57 severe]). The overall estimate of a hospitalization over time is 1 in 2,448 patients. The following tables provide an analysis of the reporting rates of these adverse events over time.

Table 1 provides US Mifeprex use and adverse reporting rates per 100,000 uses in 2-year time intervals over the past 6 years (October 2006 through October 2012).

[13] Although ongoing pregnancies (confirmed and unconfirmed) are assessed in REMS assessment reports, ongoing pregnancy is not considered a serious complication because it usually reflects an incomplete abortion which is sometimes part of the medical abortion process.

Table 1: US Reporting Rates for Serious Adverse Events with Mifeprex per 100,000 uses from October 2006 through October 2012

Time Period	Use	Adverse events	Deaths	Hospital-izations	Trans-fusions	Ectopic Pregnancies	Infection	Severe[14] Infection
10/06 to 10/08	(b) (4) K*	357	1	105	63	9	48	8
Rate per 100 K	NA	(b) (4)						
10/08 to 10/10	(b) (4) K	600	4	187	103	18	71	10
Rate per 100 K	NA	(b) (4)						
10/10 to 10/12	(b) (4) K	704	0	213	115	11	67	17
Rate per 100 K	NA	(b) (4)						

NA= not applicable
*K = 1,000; for example, (b) (4) K = (b) (4). All rates are per 100,000 uses of the drug.
Source: the data here is extracted directly from the quarterly FDA reports using the same categories.

Table 2 provides an adverse event analysis for the most recent 18 months of available data from April 30, 2011 through October 31, 2012.

[14] This category includes endometritis (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 infections and gonorrhea, cystitis and women with toxic shock syndrome not associated with a pelvic infection.

Table 2: Adverse Event Analysis - per (b) (6) US Postmarketing Adverse Event Summary from April 30, 2011 through October 31, 2012.

Time Period	~ # Women*	AEs reported	Deaths	Hospitalizations	Trans-fusions	Infections (severe)	Hospitalization Rate per women
4/30/11-10/31/11	(b) (4)	178	0	66	27	13 (5)	1 hospitalized per (b) (4) women
10/31/11 - 4/30/12		185	0	52	26	14 (3)	1 hospitalized per (b) (4) women
4/30/12-10/31/12		170	0	38	24	15 (1)	1 hospitalized per (b) (4) women

*Estimate based on above table showing (b) (4) U.S. women per month being treated with Mifeprex for termination of pregnancy from Feb 2011 through Oct 2012.

DEATHS

An overview of each of the US reports with a fatal outcome following mifepristone use for termination of pregnancy from approval in 2000 through January 9, 2013 is provided in Appendix A. Fourteen deaths in US women have been reported since approval. The last reported death occurred in March 2010. In half of the reported deaths, the cause of death was related to infection/sepsis. Two deaths were related to a ruptured ectopic pregnancy. Mifeprex is neither indicated for nor effective for terminating ectopic pregnancy.[15]

3 MIFEPRISTONE USE

3.1 MIFEPREX (MIFEPRISTONE 200MG TABLETS) UTILIZATION

Drug use information is not available to FDA through commercial databases for drugs distributed through closed distribution systems. Sales distribution data for Mifeprex is only available from the sponsor (Danco). Danco provides an estimate of the number of women who have used mifepristone in the US for termination of pregnancy on a periodic basis and as part of the REMS assessment. The (b) (6) has summarized the use data along with adverse event reporting information on a quarterly to semi-annual basis. A version of this document is available on FDA.gov (last report posted - April 2011).[16] The table below is based on the use data provided by Danco and documented in the (b) (6) summaries.

[15] "Mifeprex is contraindicated in patients with a confirmed or suspected ectopic pregnancy since Mifeprex is not effective for terminating these pregnancies." Mifeprex [package insert] New York, NY. Danco Laboratories, LLC;2005.

[16] Available at http://www fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323 htm 222. Accessed January 27, 2013.

Table 3: Estimate of the number of women who have used mifepristone in the US for termination of pregnancy per month				
End of Month/Year	Cumulative number of women from approval	Change	Number of Months	N/month
Mar 2006	575,000			
June 2006	612,000	37,000	3	12,300
May 2007	750,000	138,000	11	12,500
Jan 2008	855,000	105,000	8	13,100
Sept 2008	979,000	124,000	8	15,500
May 2009	1,100,000	121,000	8	15,100
Dec 2009	1,230,000	130,000	7	18,600
July 2010	1,350,000	120,000	7	17,100
Jan 2011	1,460,000	110,000	6	18,300
April 2011	1,520,000	60,000	3	20,000
Aug 2011	1,600,000	80,000	4	20,000
Dec 2011	1,680,000	80,000	4	20,000
Oct 2012	1,880,000	200,000	10	20,000

Danco states that the majority of drug/use ([(b) (4)]%) is distributed to/by Planned Parenthood and other family planning clinics. The remainder is distributed through hospitals and private practices. An independent study published in 2009 found 88% of Mifeprex for abortions was dispensed through clinics.[17]

3.1.1 Korlym (mifepristone 300mg tablets)

Korlym was approved without a REMS by FDA on February 17, 2012 for the treatment of Cushing's syndrome. However, the sponsor distributes Korlym through a single specialty pharmacy and agreed to provide use data as part of a PMR "to better characterize the incidence rates of adverse events with Korlym." Preliminary data from the first 6 months of marketing of Korlym indicated that [(b) (4)] patients under the care of [(b) (4)] prescribers received Korlym. Most of the use ([(b) (4)] of [(b) (4)] patients) was for the treatment of Cushing's syndrome. [(b) (4)]

[17] Finer L, Wei J. Mifepristone and abortion access in the U.S. Obstet Gynecol 2009;114:623-40.

(b) (4) Additional information on the (b) (4) code is pending.

3.2 FACTORS AFFECTING SAFE USE OF MIFEPREX

3.2.1 REMS

As described in Section 1.1, in order to obtain Mifeprex, healthcare providers must be willing to enroll in the REMS program by attesting to have the necessary skills and agreeing to comply with the program requirements. Based on the May 30, 2012 REMS Assessment submission, the following prescriber data were provided by Danco:

- Cumulative number of prescribers enrolled
- Number of new prescribers enrolled during reporting period
- Number of prescribers ordering Mifeprex during reporting period

(b) (4)

According to a study published in 2009 by Finer and Wei, between November 2000 and May 2007, among physicians who had ever provided mifepristone, 67% were obstetrician-gynecologists and 13% were family practice physicians.[17] Danco does not collect practice specialty information.

3.2.2 Planned Parenthood

Planned Parenthood and other family planning clinics account for the majority (e.g., (b) (4)) of Mifeprex use. Planned Parenthood has implemented (b) (4)

(b) (4)

[18] Fjerstad M, et al. Rates of Serious Infection after Changes in Regimens for Medical Abortion. NEJM. 2009;361-145-51.

Fjerstad et al performed a retrospective analysis assessing the rates of serious infection in the US after medical abortion. The rate of serious infection after medical abortion declined by 93% after these changes were implemented (from 0.93 per 1000 to 0.06 per 1000).[18]

In 2007, FDA stated that there was not "sufficient information to recommend the use of prophylactic antibiotics for women having a medical abortion." The current American College of Obstetricians and Gynecologists Practice Bulletin on medical abortion states that "no data exist to support the routine use of preventative antibiotics for medical abortion." The Practice Bulletin recommends oral or vaginal administration of misoprostol.[19]

The current Mifeprex professional labeling does not include information on antibiotic prophylaxis and does recommend oral (as opposed to vaginal) administration of misoprostol (in a dose different from current standard practice outlined in the ACOG Practice Bulletin and Planned Parenthood protocol).

3.2.3 Physician Training in Induced Abortion[20,21,22]

In 1996, in response to data indicating that the (1) age of practicing obstetricians who provided the majority of pregnancy terminations was rising (older than 65 years) and (2) the majority of counties in the U.S. lack of abortion providers, the Accreditation Council for Graduate Medical Education (ACGME) required obstetrics and gynecology residency programs to provide training *opportunities* in induced abortion.

In 1998 and 2004, a survey was mailed to all obstetrics and gynecology residency program directors in an effort to characterize the availability of abortion training. In 1998, 46% of respondents reported routine[23] training. In 2004, 51% of directors reported routine training, 39% reported optional training, and 10% reported no training. Of those programs with routine training, 50% reported training in termination practices -- the most common were first-trimester surgical abortion (85%), followed by medical abortion (59%), second trimester induction (51%), and dilation and extraction (36%).[20]

A survey[22] conducted in 2007 of final year obstetrics and gynecology residents sought to determine which abortion procedures residency graduates had received training. Respondents reported higher routine, on-site participation in training on surgical abortion procedures (range 65.6% - 85.2%) compared to mifepristone (52.3%). Routine participation in off-site mifepristone training was higher (72.7%). Ten percent of respondents reported that no training was available on mifepristone use, which is consistent with the 2004 study of residency program directors.

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[19] ACOG Practice Bulletin: *Compared with the FDA-approved regimen, mifepristone–misoprostol regimens using 200 mg of mifepristone orally and 800 µg of misoprostol vaginally are associated with a decreased rate of continuing pregnancies, decreased time to expulsion, fewer side effects, improved complete abortion rates, and lower cost for women with pregnancies up to 63 days of gestation based on LMP.*

[20] Eastwood KL, et al. Abortion training in United States obstetrics and gynecology residency programs. Obstet Gynecol 2006;108;303-8.

[21] Greenberg M. et al. Barriers and enablers to becoming abortion providers: the reproductive health program. Fam Med 2011;44(7):493-500.

[22] Jackson CB, Foster AM. Ob/Gyn training in abortion care: results from a national survey. Contraception 2012;86:407-417.

[23] Routine training was defined as "required training unless residents express moral objections."

The ACGME requirements for family medicine residents do not include training in medical abortion but residents must be "trained to competency" in "options counseling for unintended pregnancy." A similar survey to characterize the availability of abortion training in family medicine residencies reported 49% provide some type of abortion training.

From 1999 through 2005, the Department of Family Medicine at the University of Rochester Medical Center operated the Reproductive Health Program (RHP), a national elective abortion training program aimed to address a gap in training to all US medical students, residents, advanced practice clinicians, and physicians in practice. A study published in 2012 interviewed RHP trained providers in 2008-2009. A total of 58.8% of respondents reported providing abortions since training, with most occurring in high-volume abortion clinic settings. Of those who had provided abortions, most had performed more than 50 surgical or medical abortions. More than 90% of abortion providers reported having liability insurance that covers abortion, colleague support, ease of obtaining medications and/or equipment, reimbursement, and administrative and/or staff support at the site where they provide abortions. Relative to providers, the greatest barriers to providing an abortion reported by non-providers were lack of skills, concerns about liability, and difficulty obtaining supplies.[21] Although these data were limited to RHP trainees, data are consistent with data from other sources and provides additional insight into what facilitates abortion care and barriers.

4 CONSIDERATIONS REGARDING THE NEED FOR A REMS

4.1 SAFETY CONSIDERATIONS

In general, the intended patient population for Mifeprex is healthy. Medical abortion, similar to surgical abortion, is associated with potentially serious adverse events. Since the approval of Mifeprex, safety concerns have been identified through enhanced surveillance and reporting by certified prescribers. Use of Mifeprex is associated rarely with serious infection and hemorrhage sometimes resulting in transfusions, hospitalization, and death. Serious infections and deaths resulted in labeling changes in 2004 and 2005. There have been no new safety concerns identified with Mifeprex since that time and the serious complications being reported now are consistent with labeling. Moreover, these complications with Mifeprex are consistent with what one can expect with spontaneous abortion and surgical abortions.[24,25] The serious complications that arise can be managed if recognized in a timely manner.

(b) (6) believes that the current safety profile is reflective of an effective system in place with knowledgeable prescribers primarily using Mifeprex within that system guided by standard protocols. It is not likely that the current safe use conditions will persist to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events if the REMS was eliminated. Because Mifeprex prescribing occurs in a limited number of healthcare settings and training is not uniformly provided in physician residencies, there is no data

[24] Mifeprex [package insert] New York, NY. Danco Laboratories, LLC;2005.

[25] Grimes, DA and Raymond, EG. Medical Abortion in Adolescents, *BJM* 2011;342:d2185.

indicating that the appropriate use of Mifeprex has become an ingrained part of "standard medical practice". The "standard" is for Mifeprex to be prescribed within these family planning clinics or by qualified physicians in a private setting. However, if the REMS is eliminated, use would no longer be restricted to these practice settings with knowledgeable prescribers, and use outside the current effective "standard practice " setting could occur.

If the REMS for Mifeprex is eliminated, there would be no restrictions for dispensing and Mifeprex (or any generics that may be approved in the future) could be made available (depending on the manufacturer's business decisions) in the same manner as any prescription drug product. Such a change could result in 1) treatment delays which are problematic given the importance of gestational timing on the safe and effective use or 2) inappropriate prescribing (e.g., ectopic pregnancy) by less experienced practitioners.

4.2 MONITORING CONSIDERATIONS

It is not known how adverse event reporting will change if a REMS is eliminated. Planned Parenthood and the manufacturers would not be required to continue the same level of reporting of serious complications. Data on deaths from infection after Mifeprex use would be available through the CDC. The CDC conducts regular surveillance for maternal mortality and morbidity associated with pregnancy and abortion, including deaths from infection following a medical abortion or any pregnancy event. We note the abortion surveillance summaries published by CDC can have a lag time of up to four years.

Reporting may not be important if it was determined that the risks no longer warrant additional safe use requirements. However, given the public interest this medication generates, it is likely information inquiries will continue. If the REMS is eliminated, FDA will be less informed of adverse events that occur with Mifeprex or its generics.

4.3 DISTRIBUTION CONSIDERATIONS

The [redacted] (b) (6)) believes that Danco would continue some sort of restricted distribution even if FDA no longer requires it. It is not known how new generic sponsors/manufacturers would choose to distribute mifepristone if no restrictions were required by FDA. Even if not required and both innovator and generic manufacturers choose to continue to dispense mifepristone through clinics and medical offices, this would be based on the various manufacturers business decisions and subject to change at their discretion.

Without a REMS, prescriber and patient usage information may be more complex to obtain and less precise than the current data. Furthermore, if the sponsor(s) chose to maintain a closed distribution system, it would be difficult for FDA to track use data in the absence of being provided data directly from the sponsor(s).

4.4 CONFIDENTIALITY/PRIVACY

Confidentiality and patient privacy are significant issues with Mifeprex, but not generally a factor when determining the need for a REMS. The availability of Mifeprex through retail pharmacies could reduce patient/prescriber confidentiality by adding the need to write and fill a prescription. Concerns regarding protests or targeting may deter retail pharmacies from stocking Mifeprex.

The purpose of a REMS is to ensure the benefits of the drug outweigh its risks. While we remain concerned about confidentiality and concerned regarding the personal safety of the prescribers, pharmacists, and patients, it does not meet the criteria for requiring a REMS. Moreover, manufacturers could decide to protect prescriber and patient confidentiality without a REMS.

5 IMPACT OF REMS ELEMENTS AND THEIR REMOVAL

The risk mitigation tools that are part of the Mifeprex REMS are physician certification and controlled access (or restricted distribution). A Mifeprex prescriber must agree that he/she meets the required qualifications to assure the drug is used safely and appropriately. A prescriber self-certifies by completing a one-time enrollment form. This enrollment or certification requirement is the tool that provides controlled access to Mifeprex. Without restricted distribution, a prescriber using Mifeprex would not have to attest to having certain skills, agree to provide counseling on how to handle adverse events, provide Mifeprex during the office visit, document certain information/activities, or report serious complications.

5.1 PRESCRIBER CERTIFICATION

This Prescriber Agreement is a one-time event with limited burden. Prescriber certification probably has the most influence of the three ETASUs in addressing safe use and limiting access to Mifeprex because this element requires physicians to attest to having certain skills, agree to abide by the program requirements including reporting of serious adverse events, and complete an additional step (e.g., the enrollment form) in the usual drug procurement process.

Eliminating this element opens access to any prescriber. Therefore, it is possible that physicians and advanced practice healthcare providers (e.g., physician assistants, nurse practitioners) who are not familiar with Mifeprex and/or practice outside of facilities with established protocols may prescribe Mifeprex; a factor that could contribute to an increase in serious complications.

5.2 RESTRICTED TO CERTAIN HEALTHCARE SETTINGS

This element limits distribution by preventing the distribution of Mifeprex through retail (including mail order and internet) pharmacies. If this restriction was removed, any pharmacy could stock the drug and prescribers would no longer have to stock Mifeprex. In a "worst case" scenario, the following *could* occur:

- patients are not properly counseled about the serious complications and what to do in the event that they experience an adverse event,
- patients may not pick-up the prescription – failing to initiate the abortion in a timely manner resulting in ineffective or inappropriate use of the drug or potentially an increased incidence of complications,
- patients have difficulty finding a pharmacy that stocks the drug because not all pharmacies may choose to stock the drug, resulting in treatment delay

Although not safety concerns, confidentiality and personal safety are significant concerns with Mifeprex. Distribution through retail pharmacies could compromise patient and

prescriber confidentiality with adding a new stakeholder to the treatment process, and pharmacies could be targeted by individuals or groups opposed to abortions.

Restriction of mifepristone to certain healthcare settings is probably the most critical element for maintaining confidentiality and privacy for both patients and prescribers. This element also contributes to the patient's safe use of Mifeprex by making the prescriber responsible for giving the drug directly to the patient and counseling the patient at the time of dispensing. It is safer for the patient - providing the opportunity for direct observed therapy (although this is not a REMS program requirement) to initiate the time-sensitive abortion process, and ensures the patient leaves the healthcare facility with the medications that are necessary for completing a medical abortion to maximize efficacy and minimize risk.

5.3 DOCUMENTATION OF SAFE USE CONDITIONS

The REMS requires that prescribers review and complete a Patient Agreement with each patient before treatment is initiated. The signed Agreement is placed in the patient's medical record; however it is not collected by Danco. There is no data available on how often the Agreement is utilized.

Family planning clinics generally utilize consent forms and in this type of practice setting the Patient Agreement may be redundant. Therefore, it is not known if removing this element would increase the risk that a patient is not properly informed and counseled about complications and what to do when a complication occurs.

6 DISCUSSION

(b) (6) and (b) (6) considered two options – maintain the REMS or eliminate the REMS with the following possible rationale for each option.

- Eliminate the REMS: No new safety concerns have been identified in 6 - 7 years. The serious complications being reported now have been consistent with labeling and the reporting rate has been stable over the last several years. These complications are consistent with what one would expect with a surgical abortion and are not necessarily unique to a medical abortion with Mifeprex. Use of Mifeprex has been primarily in Planned Parenthood and other family planning clinics where there are protocols and familiarity with assessing the duration of pregnancy, diagnosing an ectopic pregnancy, performing surgical interventions in cases of incomplete abortion, and caring for patients that experience serious complications. Some of the safe use practices surrounding Mifeprex may therefore already be embedded in these practice sites that already dispensing Mifeprex and would likely be maintained even if the REMS were eliminated.

- Maintain the REMS: There have been a small number of reported serious complications associated with Mifeprex and this is likely reflective of the use of Mifeprex within a system of knowledgeable healthcare providers, safe use protocols, proper patient counseling, and follow-up procedures.

  Medical abortion accounts for the minority of abortions in the U.S. Similarly, training opportunities in medical abortion appear limited and are less available than surgical abortion experience. Given this relative lack of familiarity and

experience with medical abortion, a restricted distribution program that reinforces the necessary skills and appropriate care (i.e., counseling and follow-up) is necessary to assuring safe use of Mifeprex.

The Mifeprex REMS provides the foundation to ensure the implementation of safe use conditions with Mifeprex use. Accurate gestation dating, patient education, dispensing Mifeprex directly to the patient during the office visit, and timely access to medical care remain important to maintaining the current safety profile of Mifeprex. It is not likely that the essential safe use conditions will be maintained to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events.

7 RECOMMENDATION AND CONCLUSION

(b) (6) recommends that the existing elements of the REMS should be maintained. Specifically, prescriber certification and dispensing limited to certain healthcare settings provide a framework to ensure that the benefits of Mifeprex outweigh its risks in an appropriate patient population.

On January 30, 2013, (b) (6) and (b) (6) presented this recommendation to the Center Director and senior level management from (b) (6) There was general consensus that a REMS is necessary to ensure that the benefits outweigh its risks.

Appendix A: Overview of US Mifeprex Cases with Fatal Outcomes

State	Date of Death	Patient Age	Cause of Death	Culture if Available
(b) (6)		38	Hemorrhage from ruptured ectopic pregnancy	N/A
		18	Septic shock	CDC positively identified *C. sordellii* in uterine tissue
		21	Presumed infection	CDC positively identified *C. sordellii* in uterine tissue
		22	Sepsis	CDC positively identified *C. sordellii* in uterine tissue
		34	Sepsis	CDC positively identified *C. sordellii* in uterine cavity
		32	Not specified^ (autopsy declined)	Uterine cavity culture positive for Prevotella and Peptostreptococcus
		23	Probably methadone overdose	N/A
		24	Septic shock	Probably *C. perfringens*
		22	Suspected homicide	N/A
		23	Cocaine and Fentanyl poisoning	N/A
		18	Septic shock & cardiac arrest	*C. sordellii* confirmed in uterine samples
		29	Complications due to acute endometritis & myometritis	CDC positively identified *C. sordellii* in uterine tissue
		21	Not specified, but presumed *C. sordellii infection*	CDC positively identified *C. sordellii*
		27	Ruptured ectopic pregnancy	N/A

[A]The (b) (6) death occurred on (b) (6) (Day 33) after an initial failed surgical and medical abortion on (b) (6) (Day 1) in a woman with a large uterine fibroid. A repeat surgical abortion was done on (b) (6) (Day 22). We do not believe the death was related to the attempted medical abortion on (b) (6).

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/s/

(b) (6)

10/17/2013

(b) (6)

10/17/2013

Received concurrence from (b) (6)

Exhibit H

CONFIDENTIAL

February 4, 2016

Stephen Ostroff, M.D., Acting Commissioner of Food and Drugs
Robert M. Califf, M.D., Deputy Commissioner for Medical Products and Tobacco
Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Drs. Ostroff, Califf, and Woodcock,

The following 30 organizations write to ask the U.S. Food and Drug Administration (FDA) to lift the Risk Evaluation and Mitigation Strategy (REMS) imposed in 2000 when it approved the use of Mifeprex© (mifepristone) for pregnancy termination, and to extend the indicated use through a gestational age of 70 days. In the 15 years since mifepristone's approval, multiple clinical trials, dozens of studies, and extensive experience across the globe have confirmed the FDA's finding that mifepristone is a safe and reliable method of abortion. Studies have shown that mifepristone in combination with misoprostol is up to 99% effective for first trimester abortion[1,2] and that serious complications are rare.[3] The steady increase in use of medication abortion – now 23% of U.S. abortions – shows that many women prefer this option, and that it has the ability to improve access to abortion, even in states with restrictive laws. Provider interest in offering mifepristone has also increased substantially: in 2011, 59% of abortion providers offered early medication abortions, up from 33% in 2008.[4] This growing use of medication abortion has made a major difference in people's lives. We thank the FDA for ensuring mifepristone is available on the market for patients' reproductive health care needs.

However, many who could benefit from mifepristone still do not have access to it due to multiple types of restrictions, including those required by the FDA. In November 2015, a group of organizational and individual researchers submitted a letter to the FDA (hereinafter "Technical Letter") asking the agency to lift the REMS on mifepristone and extend the indicated use to 70 days gestational age, presenting data showing that the current restrictions and limited gestational age indication are unnecessary for the safe and effective use of the drug for pregnancy termination.

As policy, advocacy, social science, research, and academic organizations, we ask the FDA to consider the substantial evidence presented in the Technical Letter, alongside the burdens that the REMS and the label's 49-day gestational age indication place on patient access, which we describe here. The FDA held a public meeting in October 2015 to discuss improving patient access to drugs under REMS,[5] evidencing the agency's own awareness of patient burden caused specifically by restrictions imposed under REMS. We applaud these efforts and urge the FDA to use its regulatory authority to remove the medically unnecessary barriers to mifepristone.

Mifepristone underwent a lengthy approval process in the late 1990s, during which it became subject to a rarely-used approval mechanism: Subpart H of the FDA's Title 21, Chapter 314 regulations. Subpart H is used primarily for drugs with very serious and well-documented safety concerns.[6] In 2007, Subpart H restrictions on all drugs were converted automatically into a Risk Evaluation and Management Strategy (REMS),[7] a mechanism created by Congress whereby FDA can impose Elements to Assure Safe Use (ETASU). Under this law, as the Agency stated in preparation for its October 2015 meeting on REMS,[8] Congress mandated that the FDA engage in a balancing analysis to ensure that the risks mitigated by a REMS program do not unduly burden patients' access to health care:

> [E]lements to assure safe use [ETASU] ... shall–
>
> (A) be commensurate with the specific serious risk listed in the labeling of the drug;
>
> ...
>
> (C) considering such risk, not be unduly burdensome on patient access to the drug, considering in particular–
>
> (i) patients with serious or life-threatening diseases or conditions; and
>
> (ii) patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)….[9]

Although the FDA may have decided 15 years ago that the balance of risk and burden came out in favor of restricting mifepristone's indicated use and distribution, today both science and the current conditions surrounding patient access to abortion care call strongly for a reevaluation of the mifepristone label and REMS restrictions, especially its Elements to Assure Safe Use (ETASU).

We support the following changes to the mifepristone label:

- The drug should be indicated for use in medication abortions beyond 49 days gestation.
- The recommended dose regimen should be mifepristone 200 mg followed 24-48 hours later by misoprostol 800 mcg.
- The location where the patient should take these drugs should not be restricted.
- An in-person visit should be indicated as not always necessary for follow-up assessment.
- Any licensed health care provider should be able to prescribe the drug.

We expand below upon further specific changes that should be made based on scientific evidence of mifepristone's safety and efficacy, as well as the numerous burdens on patients' access to abortion care that would be greatly alleviated if the REMS were eliminated and the gestational age indication in the label were increased to 70 days.

1. **Eliminate the REMS and ETASU for mifepristone.**
   a. **Expand dispensing venues.** The ETASU state that mifepristone may only be dispensed to patients in a clinic, medical office, or hospital, and not through pharmacies.[10] The Technical Letter discusses why this requirement is not medically warranted. The requirement should be removed entirely, so that mifepristone can also be distributed via retail pharmacies like other prescription medications, in addition to being directly distributed to providers.

      This requirement significantly curtails mifepristone's potential to expand patient access to abortion care. The up-front costs (including substantial costs for pre-ordering the drug) and logistical requirements (e.g., increased staffing at provider offices) are a burden to providers and, therefore, deter some health care providers from offering medication abortion. When fewer providers are willing to stock mifepristone in their offices because of the REMS and ETASU, fewer patients can access medication abortion. In some cases this requirement may also force the patient to make an unnecessary visit to a clinic, medical office, or hospital to pick up the medication, rather than being able to pick up an order called into a pharmacy. This requirement is especially significant in underserved and rural areas where access to a health care provider is already difficult, and for those with low incomes for whom taking off work or getting to a provider multiple times in short order is impossible due to cost or family needs.[11] The Turnaway Study, a prospective longitudinal study conducted by Advancing New Standards in Reproductive Health (ANSIRH) at the University of California-San Francisco examining the effects of unintended pregnancy on individuals' lives, demonstrates that the majority of people who seek abortion care are already in difficult financial situations, and are

disproportionately people of color.[12] Costly and unnecessary visits to the doctor significantly increase financial and logistical burdens for these individuals and communities.

Any venue expansion, however, should not preclude the direct distribution of mifepristone to providers who want to dispense from their clinical settings. In many places, pharmacy refusal laws allow pharmacists to decline to fill prescriptions for reproductive health drugs such as emergency contraception and birth control, and federal policy allows providers to refuse to provide abortions.[13] So, although pharmacists' ability to dispense mifepristone would expand patient access to medication abortion in places where providers cannot easily store mifepristone in their offices, providers should retain the option to have mifepristone directly distributed to their offices to ensure continued access to medication abortion for those living in places where pharmacists can refuse to fill mifepristone prescriptions.

b. **Eliminate the Prescriber Agreement certification requirement.** Under the REMS and ETASU, providers must have a physician supervisor submit a Prescriber Agreement form to the drug's distributor attesting: 1) that mifepristone will only be provided by or under the supervision of a physician; and 2) that the physician can assess pregnancy duration, 3) diagnose ectopic pregnancies, and 4) make a plan for a patient to have surgical intervention if necessary.[10] This requirement should be eliminated for several reasons:

i. *The Prescriber's Agreement is unnecessary for the safe dispensation of mifepristone.* As the Technical Letter explains, health care professionals are already subject to many laws, policies, and ordinary standards of practice that ensure they can accurately and safely understand and prescribe medications. Provider certification is not required for health care professionals to dispense other drugs, including drugs that carry black box, or boxed, warnings about their medical risks. Accutane, for example, has a boxed warning that describes the potential risks of the drug,[14] but Accutane prescribers are not required to submit a certification form in order to prescribe it. Mifeprex also has a boxed warning[15] and there is no medical reason for a Prescriber's Agreement to be required in addition.

ii. *The Prescriber's Agreement forces providers to identify themselves as abortion providers to a centralized entity (Danco Laboratories) inspected and regulated by the FDA, which could discourage some from offering medication abortion care to their patients*. In 2014, more than half of U.S. health care facilities that provide abortions (52%) experienced threats and other types of targeted intimidation, and one in five experienced severe violence, such as blockades, invasions, bombings, arsons, chemical attacks, physical violence, stalking, gunfire, bomb threats, arson threats, or death threats.[16] Robert Dear's November 27, 2015, standoff at a Planned Parenthood health center in Colorado, which resulted in three deaths, provides one recent and chilling example of anti-abortion violence.[17] Given such escalating harassment and violence against known abortion providers,[18] clinicians may be understandably reluctant to add their names to a centralized database of mifepristone providers.

iii. *The Prescriber's Agreement would be incompatible and unnecessary if there were an expanded distribution system*. If dispensing venues are expanded as proposed in section 1a, ordinary standards of practice and state regulations would govern pharmacists' and providers' distribution of mifepristone, and a specific certification process would be unnecessary. Furthermore, a distribution system that incorporates the Prescriber's Agreement would be extremely difficult to maintain as a practical matter. Pharmacists would need to check the certification status of each prescriber before filling a prescription, which they do not normally have to do when filling other prescriptions.

Alternatively, pharmacists would need to become certified providers themselves, thus facing the deterrence problem of adding their names to a centralized database of mifepristone providers.

iv. *The Prescriber's Agreement as currently written prevents independent non-physician prescribers from being able to prescribe mifepristone without supervision by a physician*. The Prescriber's Agreement currently states that mifepristone "must be provided by or under the supervision of a physician."[19] However, nowhere in the outline piece of the REMS document written by the FDA is the word "physician" used. The REMS references only "providers" and "prescribers." [10] The Prescriber's Agreement's narrow interpretation of the REMS is medically unnecessary and severely limits patients' access to medication abortion care, because non-physician providers must work under physician supervision to prescribe mifepristone. All states give certain advanced practice clinicians prescribing authority, including for controlled substances, and 27 states allow them to dispense medications directly.[20] Advanced practice clinicians provide an increasing proportion of basic health care in the U.S., and several states authorize these clinicians to provide abortion care. If the Agreement is not eliminated, then at least enlarging the pool of health care providers that can submit the Prescriber's Agreement would help improve access and be consistent with individual state law regarding scope of practice. If the FDA does not eliminate the Agreement altogether, it should make clear that any licensed health care provider with prescribing authority is also eligible for certification to prescribe mifepristone.

c. **Remove the confusing and unnecessary Patient Agreement.** The REMS requires that each patient sign a Patient Agreement form before receiving mifepristone. This requirement is medically unnecessary and interferes with the clinician-patient relationship. It should be eliminated entirely.

In addition to being outdated and inconsistent with requirements for drugs with similar safety profiles, the Patient Agreement creates confusion for patients. Except in the few states that require that patients follow the regimen that appears on the mifepristone label, the majority of clinicians use an evidence-based regimen that is different from the regimen described in the label. Requiring a patient to sign an agreement to a treatment plan that differs from the one prescribed by her provider is confusing and could undermine trust in the clinician.

Patients have been using mifepristone safely and effectively according to evidence-based regimens recommended by their clinicians for many years, diverging from the regimen described in the Patient Agreement.[3] A wealth of data and experience since mifepristone's approval have demonstrated that this drug is extremely safe, that clinicians with routine professional training can provide it appropriately, and that patients are able to use it as directed by their health care provider.[21,22] Requiring a patient to sign an agreement to a treatment plan that differs from the one prescribed by her provider may create unnecessary confusion.

d. **Allow evidence-based follow-up assessment.** Under the Federal Food, Drug, and Cosmetic Act, the FDA should ensure that a REMS does not unduly burden patients, especially those in rural or medically underserved areas.[9] However, the documents appended to the REMS (the Medication Guide, Prescriber's Agreement, and Patient Agreement) all indicate the patient should to return to the clinic for follow-up 14 days after the patient takes mifepristone.[10] Such an in-person appointment is not always medically necessary and, when required, creates significant additional costs for patients, who must find time for another appointment at the provider's office and potentially incur substantial costs for travel, childcare, and/or lost wages.

These burdens are often increased for patients living in rural and other medically underserved areas. In 2008, 33% of all abortion patients traveled more than 25 miles to obtain care, and 74% of all patients living in rural areas traveled at least 50 miles to obtain the procedure.[23] Medical technology and telemedicine have advanced considerably since 2000,[24] and a growing body of evidence shows that alternatives to in-person follow-up, such as serum chorionic gonadotropin (hCG), multi-level pregnancy tests, and telephone counseling are safe, effective, and improve access and satisfaction for patients.[25,26,27]

2. **Increase the gestational age for indicated use on the label.**
The current label indicates use of mifepristone through 49 days after the start of the patient's last menstrual period (LMP). The Technical Letter discusses the substantial evidence demonstrating that the evidence-based medication abortion regimen is highly effective later than 49 days LMP, through at least the 10th week (64-70 days) of gestation.[28,29,30] The National Abortion Federation's (NAF) annual *Clinical Policy Guidelines*, which NAF develops by consensus based on a rigorous review of current medical literature and known patient outcomes, recommend that an evidence-based medication abortion regimen be used through 70 days LMP.[31] The time between 49 and 70 days LMP is critical for patient access, as approximately 30% of women who seek an abortion present for care during this time, according to the Centers for Disease Control.[32]

Consider the current legal and social climate

The overall legal and social climate around abortion care intensifies all of the burdens that the mifepristone REMS places on patients and makes it even more critical that the FDA lift medically unnecessary restrictions on the drug. Since mifepristone's approval, a multitude of laws and regulations at the federal and state level have dramatically restricted access to abortion care. In the first five years of this decade alone, states enacted 288 abortion restrictions – more than the entire previous decade.[33] These restrictions are typically unsupported by medical evidence and serve only to reduce access to abortion care.[34] In 2000, the Guttmacher Institute, a nonpartisan research and policy organization that seeks to advance sexual and reproductive health and rights and ensure the highest standard of sexual and reproductive health care, considered 13 states to be hostile to abortion, meaning that those states had 4-5 types of restrictions on abortion. In 2014, the number of states considered hostile had more than doubled, now including more than half of all states. [34]

Providers have increasingly been forced to close their doors as a result of mounting restrictions. There were about 1,800 abortion providers in the U.S. in 2000. Stand-alone abortion clinics constituted 447 (25%) of all providers in 2000, and those clinics provided 71% of all abortions.[35] By 2008, only 378 abortion clinics were still providing 70% of abortions.[36] Abortion clinic closures have accelerated since 2008, as lawmakers began passing restrictions at an unprecedented rate.[37] The Associated Press estimated in June 2015 that 70 abortion clinics had closed in a dozen states since 2010.[38] This wave of state restrictions and clinic closures has continued unabated in the last five years.

Some of these measures specifically block access to medication abortion by invoking the FDA-approved label. North Dakota, Ohio, and Texas currently require mifepristone to be administered solely according to the regimen that appears on the FDA label.[39] The Arkansas legislature just passed a similar law in 2015, though a federal judge issued a temporary restraining order blocking enforcement of the law until a hearing on March 14, 2016.[40] In these states, mifepristone cannot be prescribed in accordance with evidence-based practices developed in the last 15 years,[*] which improve patient access in multiple ways:

- enabling patients to take a lower dose of mifepristone, resulting in fewer side effects and lower cost;

[*]The one deviation that Texas allows from the label is one other dosage amount of Mifeprex and misoprostol.[39]

- allowing patients to take mifepristone, misoprostol, or both at home, and/or confirm termination of pregnancy at home, resulting in fewer visits to the provider;
- and offering medication abortion to patients later than 49 days LMP. [3]

Studies have also shown that these "label laws" have had a negative impact on patient access to abortion. For example, a recent study showed that after passage of laws that restricted use of mifepristone to the FDA label in Texas and Ohio, medication abortion declined dramatically while it rose in New York and California, states without restrictive laws.[41] Furthermore, these laws run counter to the FDA's own guidance, which states that a "package insert is informational only."[42,43,44] As long as the FDA-approved label diverges from evidence-based regimens, states can hide behind it as they restrict access to abortion. If the FDA does not update mifepristone's label to reflect the most current, evidence-based practice, the number of women adversely affected will only increase as additional states pass laws to exploit this discrepancy.

Other state restrictions are not specific to medication abortion, but affect all kinds of abortion care, including access to mifepristone. These medically unnecessary restrictions include the following: requirements that facilities where abortion is provided meet standards for ambulatory surgical centers; physician admitting privileges at local hospitals; and requirements that the patient and prescribing clinician must be in the same physical location, prohibiting the use of telemedicine technology. On top of these legal restrictions, anti-abortion stigma, harassment, and violence deter many health care professionals from providing abortion care. Authorizing distribution of mifepristone in pharmacies could diminish the impact of these barriers and allow providers to offer abortion care without fear of retaliation.

These restrictions, and the concomitant politicization and stigmatization of abortion care, have also seeped into other aspects of health care and prevented progress on the use of mifepristone for other indications. Removing the REMS program would make mifepristone more readily available for non-abortion therapies as well.[45,46]

In summary, the burdens on patient access to medication abortion, exacerbated by the REMS requirements placed on mifepristone, strongly outweigh any medical risk to the patient associated with the drug. In this climate of legal restrictions, clinic closures, and mounting stigma, it is increasingly important that any regulation of mifepristone be based solely on medical evidence, rather than the discretion of politicians who are determined to restrict access to abortion at any price. We recognize that the FDA is not responsible for most restrictions on abortion access. However, whenever the FDA evaluates indications and restrictions on an approved product, it does so in the context of the real-world circumstances in which the product is sold and the condition is treated. We believe this is vital in the case of mifepristone in particular, where the broad landscape of laws regulating abortion has measurable negative impact on the clinical provision of abortion care.

Mifepristone continues to hold immense promise for patient access to a safe and effective early abortion option, but medically unnecessary regulations are impeding its full potential. Extensive scientific and clinical evidence of mifepristone's safety and efficacy, and the ever-increasing burden on patient access to abortion care, clearly demonstrate that mifepristone's REMS program is not needed to protect patients. In light of the FDA's statutory mandate from Congress to consider the burden caused to patients by REMS, and the agency's own stated commitment to ensuring that drug restrictions do not unduly burden patient access, we ask that the FDA lift mifepristone's REMS and amend the label to extend the indicated use to 70 days.

CONFIDENTIAL

Sincerely,

Advancing New Standards in Reproductive Health (ANSIRH), Department of Obstetrics, Gynecology & Reproductive Sciences, University of California, San Francisco
American Civil Liberties Union
Association of Reproductive Health Professionals
Bixby Center for Global Reproductive Health, Department of Obstetrics, Gynecology & Reproductive Sciences, University of California, San Francisco
Cambridge Reproductive Health Consultants
Carafem
Center for Reproductive Rights
Center on Reproductive Rights and Justice at the University of California, Berkeley, School of Law
Feminist Majority Foundation
Guttmacher Institute
Gynuity Health Projects
Ibis Reproductive Health
Jacobs Institute of Women's Health
Legal Voice
Medical Students for Choice
NARAL Pro-Choice America
National Abortion Federation
National Advocates for Pregnant Women
National Institute for Reproductive Health
National Latina Institute for Reproductive Health
National Network of Abortion Funds
National Partnership for Women and Families
National Women's Health Network
National Women's Law Center
Planned Parenthood Federation of America
Physicians for Reproductive Health
Provide
Reproaction
Reproductive Health Technologies Project
Society of Family Planning

cc:
Valerie Jarrett, Chair, White House Council on Women and Girls
Tina Tchen, Executive Director, White House Council on Women and Girls
Jordan Brooks, Deputy Executive Director, White House Council on Women and Girls
Nancy C. Lee, M.D., Deputy Assistant Secretary of Health, Women's Health, Director of the Office on Women's Health, Department of Health and Human Services
Bobby Clark, Counselor for Public Health and Science, U.S. Department of Health and Human Services, Office of the Secretary

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Exhibit I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 29, 2016
From	(b) (6)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	20-687
Applicant	Danco Laboratories, LLC
Date of Submission	May 28, 2015
PDUFA Goal Date	March 29, 2016
Proprietary Name / Established (USAN) names	Mifeprex Mifepristone
Dosage forms / Strength	200 mg oral tablet
Proposed Indication(s)	"Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation."
Recommended:	***Approval***

1. Introduction

Mifeprex was approved for medical termination of pregnancy through 49 days' gestation on September 28, 2000, under Subpart H (21 CFR 314.520). This subpart provides for approval with restrictions that are needed to assure the safe use of a drug product shown to be safe and effective in treating a serious or life-threatening condition. The approved dosing regimen was 600 mg Mifeprex taken orally followed in two days by 400 mcg misoprostol taken orally. Mifeprex was approved with a restricted distribution plan that included a requirement that Mifeprex be provided only by or under the supervision of a physician who met certain qualifications, including the ability to date pregnancy, to identify an ectopic pregnancy, and to provide (directly or through other qualified physicians) surgical intervention in cases of incomplete abortion or severe bleeding.

The approved regimen and various alternative regimens have been studied widely, and for some years, actual US clinical practice has relied upon different doses of Mifeprex and misoprostol – i.e., 200 mg Mifeprex followed by 800 mcg misoprostol. For a time, misoprostol was primarily administered by the vaginal route; however, the occurrence of rare but lethal infections with *Clostridium sordellii* led to a change to buccal administration of misoprostol (major providers, like the Planned Parenthood Foundation of America [PPFA] also began screening for sexually transmitted infections and providing routine antibiotic prophylaxis before medical abortion). FDA has no 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 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.

This application seeks revisions to specify use of different dose and a revised dosing regimen (200 mg Mifeprex, followed in 24-48 hours by 800 mcg buccal misoprostol), and to increase the gestational age to which Mifeprex may be used to 70 days. These and other changes

requested by the Applicant are discussed in detail in Section 7.1. The Applicant's proposed changes also entail revisions to the current Risk Evaluation and Mitigation Strategy (REMS). Based on reconsideration of the need for all elements of the REMS to ensure safe use of Mifeprex, as well as on changes in FDA current practice to standardize REMS programs and materials, FDA has proposed further modifications to the REMS as well (discussed further in Sections 6.1 and 8.6.1).

2. Background

2.1 DESCRIPTION OF PRODUCT

Mifepristone is a progestin antagonist, which competitively blocks the progesterone receptor and increases the uterine sensitivity to prostaglandins. Mifeprex is used with misoprostol, a prostaglandin analog, which has uterotonic action. As the action of mifepristone increases over 24-48 hours, misoprostol is typically administered after an interval no shorter than 24 hours.

2.2 REGULATORY HISTORY

The initial approval of Mifeprex in September 2000 was based upon an application initially submitted by the then-Applicant, the Population Council in 1996. The drug was licensed to Danco Laboratories, LLC to manufacture and market in the US. The application was transferred to the current Applicant, Danco, in October 2002.

The approval came in the third review cycle, after the Applicant addressed CMC, clinical (distribution system), biopharmaceutics and labeling deficiencies satisfactorily. Mifeprex was approved under Subpart H (21 CFR 314.520), with the following restrictions on drug distribution:

> "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, provider 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."

In 2007, with the passage of the FDA Amendments Act, Mifeprex was included on the list of products deemed to have in effect an approved REMS under Section 505-1 of the Federal Food, Drug, and Cosmetic Act. A formal REMS proposal was submitted by the Applicant and approved on June 8, 2011with a Medication Guide, Elements to Assure Safe Use (ETASU), implementation system and timetable for submission of assessments. The REMS is discussed further in Section 8.6.1.

A preNDA meeting was held in January 2015 to discuss the current efficacy supplement. The Division agreed that use of published literature, under a 505(b)(2) approach, could be an appropriate way to support an efficacy supplement to make the desired changes (outlined in Section 7.1). The Division requested safety and efficacy data stratified by gestational age to support the extension of the gestational age through 70 days; the Applicant noted that safety data are not always presented in this manner. Regarding the change in what type of provider could order and dispense Mifeprex, the Applicant noted that state laws govern who is allowed to prescribe in each state. Using a more general term, like "(b) (4) would avoid specifying a particular type of practitioner. The Division stated that it would discuss this issue further internally and during the review cycle. Regarding the Pediatric Research Equity Act (PREA), the Applicant agreed it would apply to this efficacy supplement; the Applicant was advised to be familiar with language in PREA regarding extrapolation.

2.3 PRIMARY MEDICAL REVIEWERS' RECOMMENDATION FOR APPROVABILITY

The primary reviewers, (b) (6), stated in their joint review dated March 29, 2016:

The clinical reviewers recommend an approval action on this efficacy supplement.

(b) (6) did not recommend any postmarketing requirements or commitments.

Team Leader Comment:
I concur with (b) (6) recommendations.

3. CMC

No new CMC information was submitted in the efficacy supplement. (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.

During the review cycle, the Applicant submitted a chemistry, manufacturing and controls supplement (021) that provided for a new manufacturing site for the finished product, and for revised product packaging, such that the product will be provided as a single tablet packaged in the approved blister card, rather than the currently approved presentation of three tablets per blister card. The supplement was approved on March 10, 2016. Subsequently, the Applicant revised the labeling submitted to the efficacy supplement to reflect the new packaging information. (b) (6) re-evaluated the proposed labeling following this revision and concluded that it was acceptable in her second review of Supplement 020, dated March 21, 2016.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted by the Applicant. The pharmacology/toxicology review was limited to labeling; the primary Toxicology Reviewer, (b) (6) reviewed and made labeling comments on Sections 8, 12, and 13, which were conveyed to the Applicant.

(b) (6) made the following recommendation in his review dated March 4, 2016:

Conclusion: This supplement is approvable from a Pharm/Tox standpoint.

5. Clinical Pharmacology/Biopharmaceutics

5.1 CLINICAL PHARMACOLOGY REVIEW

The Applicant did not conduct any new clinical pharmacology studies pertaining to the new dosing regimen, but provided literature and one study report by (b) (4) relating to the 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 based on men and were submitted in the original NDA. The primary Clinical Pharmacology Reviewer, (b) (6) has determined that these data are appropriate for inclusion in labeling.

No drug-drug interaction studies were conducted, but (b) (6) noted that CYP3A4 inducers may have a significant effect on mifepristone PK. Because the lowest effective dose of mifepristone for medical abortion has not been determined, and because misoprostol contributes to the treatment efficacy, the impact of CYP3A4 inducers on clinical efficacy is unknown. It does not appear that misoprostol concentrations are impacted by CYP3A4 inducers.

(b) (6) stated the following in his review dated March 29, 2016:

The (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. An agreement on the language in the package insert is reached between the Sponsor and the Division on March 29, 2016 and there are no pending issues from the* (b) (6).

No post-marketing commitments or requirements were recommended.

5.2 PK AND PHARMACODYNAMICS OF DIFFERENT ROUTES OF ADMINISTRATION FOR MISOPROSTOL

Because some of the studies submitted by the Applicant in support of this efficacy supplement utilized misoprostol given by other routes of administration, I reviewed several publications on the PK associated with various routes of misoprostol administration in order to determine whether it is relevant to consider these studies as supportive, despite use of different routes of administration for misoprostol.

Two articles relating to the serum concentrations and pharmacodynamic (PD) effects of various routes of misoprostol administration were reviewed. Meckstroth 2006[1] evaluated PK and uterine response for five hours after randomizing 40 women seeking first trimester pregnancy termination to various routes of epithelial administration (rectal, buccal, dry tablets vaginally and moistened tablets vaginally). There was considerable inter-subject variability in PK for all routes of administration, although variability was non-significantly less in the buccal arm. Serum levels after both vaginal routes were much higher than for the buccal route of administration, but the uterine activity was very similar. Although no difference in adverse events between arms was noted, the study was not sufficiently powered for this outcome.

Schaff 2005[2] compared PK of buccal and sublingual administration of misoprostol and reported higher systemic levels and more frequent adverse events with sublingual administration. Uterine response was not directly evaluated in this study.

A randomized clinical trial by Middleton 2005[3] compared treatment regimens comprising 200 mg mifepristone with 800 mcg misoprostol 1-2 days later, taken either vaginally or buccally, in 442 women with gestations through 56 days. The difference in success, defined as a complete abortion without surgical intervention, was not statistically significantly different by misoprostol route of administration (buccal: 95%, vaginal 93%). The rate of ongoing pregnancy was higher for the vaginal route (1.9% vs. 0.9% for buccal); the significance of this difference was not reported.

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[1] Meckstroth KR et al. Misoprostol administered by epithelial routes. Obstet Gynecol 2006; 108: 582-90

[2] Schaff EA, DiCenzo R, and Fielding SL. Comparison of misoprostol plasma concentrations following buccal and sublingual administration. Contraception 2005; 71: 22-5

[3] 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

Team Leader Comment:
The PD data are supportive of the relevance of studies utilizing the vaginal route of administration to consideration of the proposed dosing regimen. Despite different PK profiles, it appears that the treatment effect of vaginal and buccal misoprostol is likely to be similar. Data on sublingual administration may be less generalizable due to the higher PK and adverse event frequency compared to buccal administration.

6. Consultative Reviews

6.1

(b) (6) provided recommendations to (b) (6) based on its review of the proposed modifications to the REMS. In the (b) (6) review dated March 29, 2016, the primary reviewer, (b) (6) indicated (b) (6) agreement with the following Applicant-proposed changes:

- 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."

In the course of this review, input was obtained from the (b) (6) and (b) (6) and (b) (6) considered the recent REMS Assessment data submitted by the Applicant in June 2015, postmarketing summary reporting by the (b) (6) (b) (6) safety data obtained over the past 16 years, and information about current clinical practice. Based on the information reviewed, as well as current FDA thinking about REMS language and organization, (b) (6) and (b) (6) considered the ongoing need for each REMS element to ensure that the benefits outweighed the risks of Mifeprex and proposed additional modifications to the REMS, including:

- Removal of the Medication Guide from the REMS. While the Medication Guide remains an important tool for patient education, and will still be distributed to each patient as part of labeling, it is not a necessary element of the REMS to ensure that the benefits outweighed the risks of Mifeprex
- Modification of Element to Assure Safe Use (ETASU) A, i.e., the Prescriber's Agreement. (b) (6) recommends changing the name of the document to the Prescriber's Agreement Form to be consistent with terminology used in other REMS programs. The gestational age at which Mifeprex may be used should be modified in accord with revised labeling in the Prescribing Information. References to "physician" should be changed to "healthcare provider who prescribes."
- Modification of ETASU D, i.e., the Patient's Agreement. (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
    - The established safety profile over 15 years of experience with Mifeprex is well-characterized and known serious risks occur rarely
    - 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

- The current Patient Agreement is duplicative of established clinical practice, which provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment

- Other revisions to the REMS document are recommended for consistency with changes described above and to reflect current FDA thinking and practice regarding language and flow in REMS documents. These 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.
- Modification of the REMS goals. With the recommendation for removal of the Patient Agreement, the goals statement should be revised to reflect this change. The revised goal is to ensure that prescribers are aware of the risks of serious complications associated with the use of Mifeprex and that it can only be dispensed in certain health care settings.

A full description of the (b) (6) recommendations is included in the review dated March 29, 2016. The overall (b) (6) recommendation stated:

(b) (6) *recommends the changes in the attached, redlined REMS document and materials, which represent* (b) (6) *proposed changes to the REMS as a result of this REMS Modification Review.*

Team Leader Comment:
I concur with all of (b) (6) **recommendations; Section 8.6.1 further discusses my recommendations with regard to the REMS.**

7. Clinical

7.1 OVERVIEW OF CLINICAL PROGRAM

This efficacy supplement is supported entirely by data from the published literature; no clinical trials were conducted specifically in support of the supplement. It is notable that many of the evidence-based changes proposed are reflective of how Mifeprex is actually administered in current US clinical practice. Thus, many of the studies are observational in nature, and report on the outcome of current practice.

The following are the changes requested by the Applicant:

1. Change in dose regimen (b) (4) (b) (4)
   a. Mifeprex dose decreased from 600 mg to 200 mg, taken orally on Day 1
   b. Misoprostol dose increased from 400 mcg to 800 mcg taken, and route of administration changed from oral to buccal
   c. Interval between Mifeprex dose and misoprostol dose administration and acceptable location for misoprostol administration changed; from two days (currently labeled to take misoprostol in the office on Day 3) to 24-48 hours; misoprostol to be dispensed on Day 1 to be taken 24-48 hours later at home (or other location appropriate for the patient)

   d. Provide for a repeat dose of misoprostol if complete expulsion has not occurred by follow-up

2. Change in gestational age through which Mifeprex may be used from 49 to 70 days (b) (4))
3. Change labeling regarding follow-up from specifying an in-office assessment on Day 14 to advising that patients should follow-up with their healthcare provider approximately 7-14 days after taking Mifeprex, and not specifying what assessment(s) should be performed
4. Change in labeling and REMS statements that currently provide for Mifeprex only to be supplied to, prescribed by, and administered by or under the supervision of a physician
5. Change labeling re: description of time to expulsion from 4-24 hours to 2-24 hours
6. Add misoprostol in the indication statement ("Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days' gestation.")
7. Remove the term "Under Federal law" from Prescriber's Agreement
8. Address the Pediatric Research Equity Act (PREA) requirements for pediatric studies by requesting a partial waiver in females under the age of 12 (because pregnancy does not occur in premenarcheal females) and by extrapolation from adult data bolstered by data from females under age 17
9. The Applicant also proposed conforming revisions to REMS documents based on changes requested above

Table 4 in the Appendix presents a summary of the major publications submitted and reviewed in support of the supplement. Because each publication contributes some safety and/or efficacy data for consideration of one or more given topics, this review will not follow the usual practice of discussing safety and efficacy separately, but will provide a topic-centered discussion of the totality of the data.

Certain changes (6 and 7 above) entail regulatory decisions that are not based upon review of data; these are discussed in Section 7.7. Other changes, necessitated by compliance with current labeling standards such as the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR), are discussed in Section 12.

The original approval of Mifeprex was based on data from one US trial and two French trials. The US data included 827 women with gestations $\leq$ 49 days, and showed a 92.1% success rate, with success defined as complete expulsion of products of conception (POC) without need for surgical intervention. Of cases that did receive surgical intervention, 1% had ongoing pregnancies, while 4.7% had incomplete abortions (pregnancy terminated, but POC not completely expelled). The French studies included 1,681 women and showed overall success in 95.5% of women, with 1.3% having ongoing pregnancy and 2.9% receiving surgical intervention for incomplete abortion.

The studies reviewed in the succeeding sections include the proposed regimen where noted, while some studies are based on regimens that vary from that proposed (e.g., vaginal misoprostol, lower misoprostol dose). As discussed in Section 5.2, PK, PD and clinical data indicate the relevance, particularly of data on vaginally-administered misoprostol. Unless specifically noted, the definition of success for the treatment regimen is defined as complete expulsion of the pregnancy without need for surgical intervention for any reason. Where the rate of ongoing pregnancy is discussed as an outcome measure, this refers to identification of an ongoing pregnancy during follow-up, typically by ultrasound.

7.2 CHANGE IN DOSING REGIMEN

In general, studies of treatment regimens evaluated specified regimens of mifepristone and misoprostol (i.e., they did not study varying doses and routes of administration as individual elements). For this reason, the review will discuss studies that support the proposed revised doses of Mifeprex and misoprostol and the buccal route of administration of misoprostol as a single topic. Some studies did specifically evaluate the dosing interval between mifepristone and misoprostol or the home administration of misoprostol, so these studies are discussed as separate topics.

7.2.1 Revised dose for Mifeprex and revised dose and route of administration for misoprostol

There is a substantial body of literature supporting the proposed dosing regimen, which includes a lower dose of Mifeprex and a higher dose of misoprostol compared to the currently labeled regimen, and a change from oral to buccal administration of misoprostol.

Four studies and one systematic review evaluated the exact proposed dosing regimen through 70 days gestation. These include three prospective observational studies (Winikoff 2012[4], Boersma[5], Sanhueza Smith[6]) and one randomized controlled trial (RCT) (Olavarrieta[7]) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin[8] covered 20 studies, all but one of which 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%. Many of these papers also provided success rates stratified by week of

[4] 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

[5] 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

[6] 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

[7] 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

[8] Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015; 126(1): 12-21

gestation; these are discussed in Section 7.3. The large systematic review[8] of over 33,000 women through 70 days gestation provided information on rates of serious adverse events and reported rates of infection ranging from 0.01-0.5%, transfusion from 0.03-0.6% and hospitalization from 0.04-0.9% (see Section 8.1).

A number of additional studies assessed the proposed regimen through 63 days gestation, overall success rates ranged from 91-99.6%, with most in the 96-97% range. A few studies included only earlier gestational ages, e.g., through 56-59 days, and reported success rates from 92-98%, with ongoing pregnancy rates under 1%. Again, many of these papers provide success rates stratified by week of gestation, which are shown in Table 4 under the heading "Increased Gestational Age." Safety findings from this group of publications included a finding that fever/chills were more frequent with buccal vs. oral misoprostol (Winikoff 2008[9]) and a similar finding of higher non-serious adverse events (e.g., vomiting, fever/chills) for the 800 mcg vs. a 400 mcg dose of misoprostol (Chong 2012[10]), while Middleton[3] reported similar rates of common adverse events for buccal and vaginal misoprostol, with the exception of diarrhea, which was higher in women receiving misoprostol buccally. Raymond's systematic review[11] of global studies included over 45,500 women, of whom 2,200 received misoprostol doses ≥ 800 mcg, and reported rates of hospitalization of 0.3% and of transfusion of 0.1% in the population overall. The large US observational study (Gatter[12]) of over 13,000 women through 63 days gestation reported rates of infection that required hospitalization of 0.01%, and transfusion of 0.03%, while a large Australian observational study (Goldstone 2012[13]) reported rates of known/suspected infection of 0.23%, and of hemorrhage of 0.1%. Finally, a study (Ireland[14]) that compared over 30,000 women undergoing medical vs. surgical abortion through 63 days reported non-significantly different rates of a composite outcome including hospitalization, emergency department visit, infection and transfusion, with a total rate over the entire population of 0.1%.

Other relevant publications include the systematic review by Raymond[11] of 87 studies, which covered a variety of misoprostol doses and routes of administration used with 200 mg of

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[9] 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

[10] 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

[11] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

[12] 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

[13] 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

[14] 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

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%. The paper by Kulier[15] presents a Cochrane systematic review of 58 studies comparing different doses of mifepristone and misoprostol, which concluded that the 200 mg dose of mifepristone is as effective as the 600 mg dose, and that oral misoprostol is less effective than vaginal misoprostol, while buccal is as effective as vaginal but has a higher frequency of adverse events. Raghavan[16] used a 400 mcg dose of buccal misoprostol along with 200 mg mifepristone and reported a success rate of 97.1%.

Data for all relevant studies are provided in Table 4.

Team Leader Comments:

- **The available data support the safety and efficacy of the new proposed dosing regimen, including the revised doses of Mifeprex and misoprostol and the buccal route of administration for misoprostol.**
- (b) (4) **However, there are no safety or efficacy concerns about the originally approved dosing regimen that led to removing this regimen from labeling.**

7.2.2 Revised time and location for misoprostol dosing

Dosing Interval

The interval between the dose of Mifeprex and the misoprostol administration is currently described as two days; the supplement proposes to modify this to "24 to 48 hours." Allowing for a broader range in the dosing interval gives the woman more flexibility, and may shorten the time to complete abortion, since this usually follows fairly rapidly after misoprostol administration (see Section 7.6).

Studies supporting the new dosing regimen described in the preceding section used the proposed dosing interval unless otherwise specified. In addition, data specifically supporting the new interval were provided in a review article by Wedisinghe[17], which identified five RCTs, four of which used the proposed dose (Creinin 2004[18], Creinin 2007[19], Guest 2007[20]

[15] Kulier R, Kapp N, et al. Medical methods for first trimester abortion (Review). The Cochrane Library 2011, Issue 11: 1-126

[16] 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

[17] 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

[18] 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

[19] Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, and Meyn LA. Medical Abortion at the Same Time (MAST Study Trial Group). Mifepristone and misoprostol administered

and Schaff 2000[21]), although in all four, the misoprostol was administered vaginally. Three of the studies included gestations through 63 days; Schaff included gestations through 56 days. Intervals compared included simultaneous administration of misoprostol after Mifeprex vs. 24 hour interval, 6 hours vs. 36-48 hours, 6-8 hours vs. 23-25 hours, and 1 day vs. 2 days vs. 3 days. Rates of successful terminations were equivalent based on statistical tests of non-inferiority. 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. Safety data were not reported in this review.

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 difference remained statistically significant, with greater success for the 24-48 hour dosing interval, when the data were stratified by gestational age (≤ 49 days and 50-63 days). However, the overall rate of ongoing pregnancies did not differ significantly by dosing interval. Safety data were summarized in this review, but not discussed with respect to dosing interval.

Team Leader Comment:

The proposed dosing interval allows for earlier administration and an expanded window over which misoprostol may be taken, while maintaining the originally labeled timing for misoprostol administration as the upper limit of the interval. The available data support that the efficacy of the treatment regimen is not compromised by revising the dosing interval to 24-48 hours.

Home Administration of Misoprostol

In the review cycles for the original approval of Mifeprex, FDA originally considered allowing the option of taking misoprostol either at home or at the prescriber's office; however, re-review of the data provided at that time led to the determination that the data did not provide substantial evidence of safety and efficacy for home administration. Nonetheless, in current clinical practice, it is common to provide the woman with misoprostol (or a prescription for misoprostol) at her initial appointment (at which the Mifeprex is administered) and allow her to take it at home at the appropriate time. In this submission, the Applicant has submitted additional data in support of administration of misoprostol at a location convenient to the woman. While no studies specifically evaluated treatment outcomes for home vs. clinic dosing of misoprostol, the studies listed in Table 4 under the heading "Home Dosing of Misoprostol" all included home dosing of a mifepristone

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simultaneously versus 24 hours apart for abortion a randomized controlled trial. Obstet Gynecol 2007; 109: 885-894

[20] Guest J, Chien PF, Thomson MA and Kosseim ML. Randomized controlled trial comparing the efficacy of same-day administration of mifepristone and misoprostol for termination of pregnancy with the standard 36 to 48 hour protocol. BJOG 2007; 114: 207-15

[21] Schaff EA, Fielding SL, Westhoff C et al. Vaginal misoprostol administered 1, 2 or 3 days after mifepristone for early medical abortion: A randomized trial. JAMA 2000; 284: 1948-53

and misoprostol dosing regimen as part of the treatment regimen. One study and one literature review included women with gestations through 70 days. The majority of the studies used the proposed regimen; a few used vaginal misoprostol, which is considered relevant for reasons previously discussed.

The Raymond systematic review[11] of 87 studies with over 45,000 women included 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. A logistic regression analysis of factors leading to increased failure found no evidence that home use of misoprostol increased rates of treatment failure rates or serious complications.

Therefore, the efficacy and safety data provided in those studies support the proposal that misoprostol does not need to be restricted to in-clinic administration to provide a safe and effective medical abortion using the proposed dosing regimen. Given the rapid onset of bleeding and cramping after taking misoprostol, allowing home administration increases the likelihood that the woman will be in an appropriate location when the process begins.

Team Leader Comment:

The available data support the safety and efficacy of the proposed treatment regimen, regardless of the location in which misoprostol is taken.

7.2.3 Option for an additional misoprostol dose

Although Reeves[22] reports that fewer than 5% of women taking Mifeprex and vaginal misoprostol will have a persistent gestational sac one week after using Mifeprex, it is important to know whether all such cases require surgical intervention, or whether a second dose of misoprostol may result in a complete abortion. The Reeves[22] publication pooled data from two RCTs (Creinin 2004[18] and 2007[19]) in which women who had not expelled the gestational sac per a sonographic assessment 6-11 days after taking Mifeprex received a second vaginal dose of misoprostol. Of 68 women with persistent gestational sac, 62% had a complete abortion per a follow-up ultrasound one week after the second dose of misoprostol. Of 14 women who had an ongoing pregnancy (as determined by fetal cardiac activity at initial follow-up), 63% no longer showed fetal cardiac activity following the second dose.

A number of other studies included the option for a second dose of misoprostol as part of the evaluated treatment regimen. Indications for an additional dose include no bleeding within a specified time after the first misoprostol dose or a finding of an incomplete abortion at follow-up. Studies that specifically report the success rate of a repeat dose of misoprostol are:

- Winikoff 201[24] – 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.

[22] Reeves MF, Kudva A and Creinin M. Medical abortion outcomes after a second dose of misoprostol for persistent gestational sac. Contraception 2008; 78: 332-5

- Chen and Creinin 2015[8] – 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 2015[5] – 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 2014[23] – 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 2012[10] – 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 2008[9] – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%

Three other studies (Bracken 2014[24], Coyaji 2007[25], and Raghavan 2011[16]) are less relevant because they evaluated a 400 mcg dose of misoprostol, but these studies still reported high success rates for a second dose. In Bracken, gestational-age stratified success rates after a second dose were 90.9% for gestations from 57-63 days and 86.3% from 64-70 days among the 6-11% of women who took a second dose; in Raghavan, they were 97% for gestations of ≤ 49 days and 100% for gestations of 50-63 days; and Coyaji reported 86% success overall.

Safety reporting over all of these studies did not specifically address safety findings in the subset of women who received a second dose, but there were no unexpected safety findings overall. The Gallo 2006[26] systematic review of studies that included more than one dose of misoprostol (varying dosing regimens) provided further safety data that are discussed in the primary review.

Team Leader Comments:

- **A finding of an incomplete abortion could indicate an ongoing pregnancy or that the pregnancy has been terminated but that the woman has not yet fully expelled the products of conception. The Applicant indicates that only about 1-5% of women will need a second dose of misoprostol following the initial Mifeprex treatment regimen.**
- **The available data support the safety and efficacy of a repeat dose of misoprostol if complete expulsion of the products of conception has not occurred but the pregnancy**

[23] 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

[24] 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

[25] 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

[26] 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

is not ongoing. The relatively high success rates after a second dose indicate that this option is likely to reduce the need for a surgical intervention. While there is a suggestion that the success rate following a second dose of misoprostol may be somewhat lower at more advanced gestational ages, there is no evidence that the practice of offering an additional dose results in adverse effects.

- **Surgical evacuation of the uterus is still recommended in labeling in the case of an ongoing pregnancy.**
- **The labeling will not specify how follow-up will be performed; that will be a decision made between the healthcare provider and patient. Based on the results of a number of studies that evaluated the utility of symptom questionnaires and home pregnancy tests, the healthcare provider and patient can safely determine if it is likely that she has not had a complete abortion. Current professional guidance (American College of Obstetricians and Gynecologists Practice Bulletin 143[27]) provides recommendations on making this determination. In the case where it is determined that an incomplete abortion is likely, the patient would come in for a visit and discuss options, including a second dose of misoprostol if the pregnancy has been terminated but she has not completely expelled all products. As noted, in the case of an ongoing pregnancy, surgical termination is recommended.**

7.3 CHANGE IN GESTATIONAL AGE

The Applicant submitted four studies through 70 days gestation using the proposed regimen, one of which was in the US, for a total of 2,994 women ≤ 70 days. Also relevant is a global systematic review of 20 studies, all but one using the proposed regimen. Three of the studies also allowed for a repeat dose of misoprostol if needed.

- In the three studies (Winikoff 2012[4], Boersma[5] , Sanhueza Smith[6]) evaluating efficacy by gestational age, rates for 64-70 days were 91.2, 92.8 and 96.2%, respectively.
- The fourth study (Olavieretta[7]) used the proposed regimen to determine efficacy when non-physician providers were used; efficacy through 70 days was 98.4% with physician providers and 97.9% with nurse providers.
- The systematic review (Chen and Creinin[8]) provided a pooled success rate for 64-70 days of 93.1%; a total of 33,846 women were ≤ 70 days.
- Another systematic review (Abbas[28]) of various regimens included an arm with the proposed regimen, with a rate at 64-70 days of 92.5% in that arm.

There are two more studies through 70 days that used regimens that deviated from that proposed but are relevant because these doses and routes of administration are expected to have similar or lower effectiveness.

- One (Gouk[29]) used 800 mcg vaginal misoprostol; the success rate was 94.5% at 64-70 days

[27] 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.

[28] Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70 days gestation. Contraception 2015; 92: 197-9

- One (Bracken[24]) used 400 mcg sublingual misoprostol; the success rate was 91.9% at 64-70 days; although this is a lower dose than proposed, the PK concentrations of misoprostol are higher after sublingual dosing[2], so it is difficult to determine if the efficacy reported in this study is generalizable to the proposed regimen

Therefore, overall, the efficacy at 64-70 days appears to be in the range of 91-98% for the proposed regimen.

While not all studies thoroughly discussed adverse events, those that reported did not have unexpected rates of serious or common adverse events (see additional discussion of safety in Section 7.2.1).

Additional studies included women at gestational ages greater than the currently approved 49 days but < 64 days; these are listed in Table 4 under the heading "Increased Gestational Age."

Team Leader Comments:

- **The available data support the safety and efficacy the proposed regimen for use in gestations through 70 days.**

7.4 CHANGE IN FOLLOW-UP

Current Mifeprex labeling states that "Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex." The Applicant proposes that a more flexible follow-up regimen is safe and effective; proposed labeling would state "Patients should follow-up with their healthcare provider approximately 7-14 days after the administration of Mifeprex."

The impact of the timing of follow-up was assessed in Raymond's systematic review[11] of studies using various treatment regimens through 63 days gestation. 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 < one week after Mifeprex vs. a week or more after Mifeprex.

The primary reviewers discussed the extensive data on various follow-up options that may be used to identify those women who warrant further evaluation and possibly further intervention. Studies in Table 4 under the "Method of Follow-up" were considered, and include a variety of study designs and regimens through 63 days gestation. For this topic, the specific regimen studied is less important, because there is no reason to presume that a particular follow-up strategy would be differentially accurate for different treatment regimens. Overall, it appears that various methods of follow-up, including home pregnancy testing and phone contact during which the patient is queried about symptoms (bleeding, etc.), are acceptable alternatives to in-clinic follow-up.

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[29] Gouk EV et al. Medical termination of pregnancy at 63-83 days gestation. British J Obstet Gyn 1999; 106: 535-539

Team Leader Comments:

- **The Raymond analysis[11] of 87 trials finding no difference in failure rates for earlier (< one week) vs. later (≥ one week) follow-up supports the broadened window proposed for follow-up.**
- **The available data support the proposal that there are a variety of follow-up modalities that can adequately identify the need for additional intervention, not all of which require in-clinic assessment of the patient.**
- **The labeling will not be directive regarding specific details of how follow-up will be performed; that will be a decision made between the healthcare provider and patient.**

7.5 CHANGE IN PROVIDER

The current labeling states that Mifeprex "should be prescribed only by physicians" and the 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 dispense/administer Mifeprex to patients. The Applicant now proposes changes to the labeling and REMS to permit other healthcare providers, such as nurse practitioners, certified nurse midwives, and physician assistants, to order, prescribe, dispense, and administer Mifeprex. The language proposed by the Applicant for this broadened category of providers was "(b) (4) The data supporting such a change are discussed here.

Three RCTs (Olavarrieta 2015[7], Kopp Kallner 2015[30] and Warriner 2011[31]) and one comparative study (Puri 2015[32]) addressed the safety and efficacy of medical abortion when performed by non-physician healthcare providers. All used the proposed dosing regimen, except Warriner, who studied vaginal misoprostol. Almost 1,500 women (over 700 of whom had non-physician care) had gestations through 70 days or more, while the Kopp Kallner and Warriner studies include almost 2,300 women (over 1,000 of whom had non-physician care) with gestations up to 63 days. Success rates are ≥ 96%, regardless of gestational age, and very similar across provider types, and across all studies, the single report of serious adverse events concerned a physician-treated woman who was hospitalized for bleeding (Olavarrieta[7]).

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[30] 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

[31] 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

The Warriner study is described in the Renner 2013 systematic review discussed in the primary review; because this is the only study in that systematic review that evaluated medical (rather than surgical) abortion, I discuss that study directly here.

[32] 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

Team Leader Comments:

- **The available data support the safety and efficacy of allowing certain non-physician healthcare providers to order, dispense and administer Mifeprex, provided they meet the requirements for certification described in the REMS.**
- **However, the Division was concerned that the Applicant's proposed terminology ("(b) (4) was non-specific, as there are many types of (b) (4) (b) (4) The Division and (b) (6) propose use of the term "healthcare provider who prescribes." Use of this terminology will include other practitioners who prescribe; in addition, this phrase is consistent with language in the statute. This wording will limit healthcare providers who may become certified under the REMS to those who are licensed in their state to prescribe medications. The specific practitioners to whom this terminology applies will be defined on a state-by-state basis, as state laws regulate prescribing abilities of various healthcare practitioners.**

7.6 CHANGE IN TIME TO EXPULSION

The Applicant proposed to change the description in labeling of the time between misoprostol administration and expulsion of the products of conception from "4-24 hours" to "2-24 hours."

Winikoff 2012[4] provided data using the proposed regimen for gestations at 57-63 days and at 64-70 days demonstrating that by five hours post-misoprostol, about 50-60% of women have expelled the products of conception; expulsion began shortly after dosing and was virtually complete by 24 hours. Women in the earlier gestational age group were more likely to expel sooner (for example, the proportion of women with expulsion at three hours was significantly higher in the 57-63 day group than the 64-70 day group). Other studies (Lohr[33] [which administered misoprostol 5 minutes after Mifeprex], Creinin 2004[18] and 2007[19] [which used vaginal misoprostol]) addressing the time of expulsion did not use the exact proposed regimen, but similarly found that the average onset of cramping was 1.5-2 hours and onset of bleeding was 2-3 hours after misoprostol dosing.

Team Leader Comment:

The available data support the revised statement about the typical time frame for expulsion after misoprostol dosing. Accurate information will help the patient ensure that she is in an appropriate setting when expulsion is likely to occur.

7.7 REGULATORY CHANGES

7.7.1 Addition of Misoprostol to the Indication Statement

The Mifeprex labeling currently states in the indication statement of the Indication and Use (I&U) section:

> Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

Reference to misoprostol is made in this section several sentences later, in the statement:

[33] 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

> Patients taking Mifeprex must take 400 mcg of misoprostol two days after taking mifepristone unless complete abortion has already been confirmed before that time.

The Applicant proposed to include misoprostol in the actual indication statement, as follows:

> Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days' gestation.

The other explanatory statements in the I&U section will be moved to other appropriate sections of labeling (e.g., Dosing and Administration, Warnings and Precautions).

Team Leader Comments:

- **I agree with the proposed addition of misoprostol to the indication statement. All of the data reviewed for this supplement and for the original Mifeprex application was based upon a combined regimen of the two drugs. In addition, reference is made throughout labeling to use of misoprostol as part of the combined regimen. Further, this is 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."**
- **As with other products used concomitantly with another drug that is referenced in the labeling, the Mifeprex labeling will refer the reader to misoprostol labeling for specific information on that drug.**

7.7.2 Removal of "Under Federal law"

This term is used in two places in the Prescriber's Agreement:

> Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications…
>
> Under Federal law, each patient must be provided with a Medication Guide.

The Division and (b) (6) researched the origin of this language in the REMS, and neither was able to determine a specific clinical rationale for its inclusion. The phrase appears redundant, because all of the requirements under the REMS are imposed as a matter of Federal law. Per the (b) (6) review, there is no precedent for use of this term in other REMS documents.

Team Leader Comment:

I agree that the term "Under Federal law" should be removed from the Prescriber's Agreement.

8. Safety

As noted earlier, the discussion of particular topics relating to proposed changes in the regimen includes review of both efficacy and safety data. More general safety information is addressed in this section.

Exposure to the proposed regimen, as demonstrated in the literature for various topics, is shown in Table 1. Although supportive data from variants on the proposed regimen was also reviewed, this table refers only to studies evaluating the exact proposed regimen, with the exception of the follow-up topic, because the specific regimen used is not expected to impact the data obtained on the utility of various follow-up methods. In addition, while of considerable value, data from systematic reviews or meta-analyses are not included here because they may result in repeat counting of subjects from individual studies. There are

additional studies that allowed the option of an additional dose of misoprostol, but only those studies that clearly reported the effectiveness of that second dose are listed here. It should be noted that only a single study provided age-stratified efficacy data that included females under age 18, but a number of studies included pregnant females below the age of 18 in their overall study population.

Table 1 Number of Studies and Subjects by Topic and Region

Topic	US Data # of studies (N)	International Data # of studies (N)
Revision of Dosing Regimen (doses of mifepristone and misoprostol, route of administration for misoprostol, dosing interval)	7 (16,794)	15 (18,425)
Home Use of Misoprostol^	3 (1,728)	5 (15,896)
Additional Dose of Misoprostol*	2 (34)	4 (21+)
Gestational Age 63-70 days	1 (729)	3 (2,392)
Method of Follow-up	3 (1,709)	7 (6,159)
Time of Follow-up	0	1 (45,528)
Change in Healthcare Provider	0	3 (1,222 with non-MD provider)
Use in Adolescents#	1 (322 ≤ 16 years, 283 17 years)	0

^Data shown here represent only studies in which success after home use was specifically reported; many other studies included home dosing of misoprostol as part of the treatment regimen

*** Data shown in this row represent only the number of subjects for whom efficacy of the second dose was specifically reported; as noted previously, many studies included the option of a second dose, but did not specifically address the number of women who received a repeat dose. Given that about 1-5% of women may be eligible for a receiving a second dose, the number treated with a second dose is likely markedly higher than what is shown here.**

#This number is based only on the Gatter study[12], which provided age-stratified efficacy data. However, other studies did include females under age 17.

Team Leader Comment:
The volume of evidence supporting each of the proposed changes is acceptable.

8.1 SERIOUS ADVERSE EVENTS

Deaths and Serious Adverse Events

Death in association with abortion is extremely rare. Recent CDC information[34] reports a fatality rate for legal abortion (medical and surgical) over 2003 to 2011 to be 0.73 per 100,000 abortions. In the current submission, most articles did not specifically comment on deaths, possibly because this is such a rare outcome. Of seven US studies, only Grossman 2011[35] reported on deaths, noting 0 deaths among almost 600 women who received the proposed regimen through 63 days gestation. An additional Australian study (Goldstone

[34] http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6410a1.htm?s_cid=ss6410a1_e.

[35] Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. Obstet Gynecol 2011;18:96-303

2012[13]) of the proposed regimen used through 63 days reported a single death among 13,345 medical abortions (0.007%).

While not all studies provided information on serious adverse reactions associated with the Mifeprex regimen, the primary review 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 are as follows:

- Hospitalization: 0.04-0.6% in US studies of over 14,000 women; 0-0.7% in international studies of over 1,200 women
- Serious infection/sepsis: 0-0.2% in US and international studies of over 12,000 women
- Transfusion: 0.03-0.5% in US studies of over 17,000 women; 0-0.1% in international studies of over 12,000 women

Upadhyay[36] 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.

Team Leader Comment:
Overall, the rate of deaths and SARs is acceptably low and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen.

8.2 OTHER ADVERSE EVENTS

8.2.1 Common AEs

Examination of the common adverse reaction data by US vs. non-US study location revealed that there were differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the US 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-US studies. Regardless, inclusion of this non-US data in labeling would not be appropriate, as it is unlikely to be informative to the US population of users. The data to be reported in labeling is shown in Table 2.

[36] 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

Table 2 Common Adverse Events (≥ 15%) in US Studies of the Proposed Dosing Regimen

Adverse Reaction	# US 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[3], Winikoff[4] and Winikoff[9]

Team Leader Comment:
The Applicant noted that bleeding and cramping are part of the expected effect of the treatment regimen, and therefore were not typically ascertained or reported as adverse reactions. I agree that it is appropriate to exclude these effects from labeling in Section 6.1.

8.3 SUBMISSION-SPECIFIC SAFETY ISSUES

8.3.1 Uterine Rupture

As discussed in the primary 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 > 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 (b) (6) and the (b) (6) ((b) (6) reviewed the literature and (b) (6) searched FAERS for adverse event reports. The literature review identified two studies in first trimester gestation that evaluated the risk of uterine rupture in over 500 women who received 800 mcg of misoprostol to evacuate the uterus. Although 144 women in the studies had a previous uterine scar (a known risk factor for uterine rupture), no ruptures occurred in either study. Three case reports of uterine rupture with mifepristone/misoprostol treatment in the first trimester were identified (see Table 3).

Table 3 Case Reports of Uterine Rupture with Mifepristone/Misoprostol in the First Trimester

Study	GA (weeks)	Mifepristone used?	Dose of Misoprostol	Number of doses of misoprostol	Risk Factor for Rupture
Khan[37]	8	Yes; dose not specified	600 mcg	1	1 prior C-section, 1 prior uterine rupture at 32 weeks
Bika[38]	10 2/7	Yes; 200 mg	800 mcg x 2 doses then 400 mcg x 2 doses	4	2 prior C-sections
Willmott[39]	12 3/7	Yes; 200 mg	400 mcg	5	none

Source: modified from (b) (6) table in the primary review

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.

Team Leader Comment:
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 warranted, but no restriction of use is needed based upon this extremely rare adverse reaction.

8.4 LABORATORY TESTING & VITAL SIGNS

The studies evaluated did not describe laboratory testing or evaluation of vital signs. Lab tests that are commonly performed for medical abortion include confirmation of pregnancy (urine or serum pregnancy testing) as well as Rhesus factor testing, such that RhD immunoglobulin can be administered as indicated.

8.5 POSTMARKETING SAFETY FINDINGS

There is a substantial amount 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.

[37] 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

[38] 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

[39] 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

In addition, the (b) (6) (b) (6) provided a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. There have been 18 reported deaths in the US, with eight of these associated with sepsis (seven tested positive for *Clostridium sordellii,* one tested positive for *Clostridium perfringens).* Seven of the eight cases involved vaginal use of misoprostol, a practice that is no longer common. There have been an additional 11 foreign deaths reported in this time period, including three in which *Clostridium* was identified. There have been no Clostridial septic deaths reported in the US since 2009, and none worldwide since 2010.

(b) (6) also updated case reports of serious adverse events over the same time period, although this entailed search of two FDA adverse events databases (the previous system, AERS, and the current FAERS), which precludes providing cumulative numbers over the full time period. Details are provided in the primary review. In summary, these data demonstrate that the rates of hospitalizations, severe infections, blood loss requiring transfusion and ectopic pregnancy remain stable and acceptably low.

During its ongoing surveillance of adverse events, (b) (6) did identify a safety signal of anaphylaxis and angioedema, with one case of anaphylaxis reported a few hours after mifepristone administration, and six cases of angioedema, five of which occurred in the context of pregnancy termination, within 24 hours of mifepristone administration (the sixth was in a Cushing's syndrome patient). There were no additional cases reported in the literature.

Team Leader Comment:
I agree with (b) (6) recommendation that anaphylaxis and angioedema be described in the Contraindications and Adverse Reactions sections of labeling and for continued pharmacovigilance for these adverse events.

8.6 SPECIAL ISSUES RELATIVE TO THIS NDA

8.6.1 REMS Modifications

As discussed previously, the current REMS consists of the following elements:

- Medication Guide
- Elements to Assure Safe Use (ETASU)
    - ETASU A: Special certification of healthcare providers who prescribe Mifeprex, completion of a Prescriber's Agreement and enrollment in the REMS program
    - ETASU C: Mifeprex dispensed only in certain healthcare settings (clinics, medical offices or hospitals) by or under the supervision of a specially certified prescriber; not distributed to or dispensed through retail pharmacies
    - ETASU D: Patients must complete and sign a Patient Agreement; a copy to be placed in the patient chart and a copy of the Agreement and the Medication Guide to be provided to the patient
- Implementation system: Distributors of Mifeprex must be certified and agree to ship Mifeprex only to locations identified by certified prescribers.

After review of the modifications proposed by the Sponsor, the modifications that would be needed to harmonize with planned labeling changes, and after broad discussion of the need

for various elements of the current REMS, (b) (6) recommended and the Division agreed to the following, for reasons that are discussed in Section 6.1:

- Removal of the phrase "under Federal law" from the Prescriber's Agreement (Prescriber's Agreement Form) (see further discussion of this change in Section 7.7.2)
- Replacement of references to "physician" with "healthcare provider who prescribes" (see further discussion of this change in Section 7.5)
- Removal of the Medication Guide from the REMS – (b) (6) agrees that distribution of the Medication Guide as part of patient labeling will ensure that patients receive this educational tool, and that requiring provision of the Medication Guide under the REMS is not necessary
- Revision of the Prescriber's Agreement (now called the Prescriber's Agreement Form) – the requirement for certification remains, and the criteria that a provider must meet to become a certified prescriber have not changed. The provider reporting requirement has been changed to mandate reporting only of deaths (currently reporting of ongoing pregnancies, hospitalizations, transfusions or other serious adverse events is required). Reference to the Patient Agreement should be removed.
- Removal of the Patient Agreement form – (b) (6) concurs with the recommendation for removal of the Patient Agreement from the REMS, for the reasons outlined in the (b) (6) review. In addition, 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. FDA has removed REMS requirements in other programs based on the integration of the REMS safe use condition into clinical practice.
- Revision of the REMS goals to state that the goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by a) requiring healthcare providers who prescribe to be certified in the Mifeprex REMS program, and b) ensuring that Mifeprex is only dispensed in certain healthcare settings under the supervision of a certified prescriber

8.6.2 Advocacy Group Communications

The Agency received three letters from representatives from academia and various professional organizations, including the American Congress of Obstetricians and Gynecologists, the American Public Health Association (APHA), the National Abortion Federation (NAF), Ibis Reproductive Health and Gynuity. In general, these advocates requested FDA to revise labeling in a manner that would reflect current clinical practice, including the new dose regimen submitted by the Sponsor, and proposing to extend the gestational age through 70 days. Other requests were that the labeling not require that the drug-taking location for both Mifeprex and misoprostol be restricted to the clinic, and that labeling not specify that an in-person follow-up visit is required. The advocates also requested that any licensed healthcare provider should be able to prescribe Mifeprex and that the REMS be modified or eliminated, to remove the Patient Agreement and eliminate the prescriber certification, while allowing Mifeprex to be dispensed through retail pharmacies. The letters cited articles that were also submitted by the Applicant and are reviewed above.

8.7 OVERALL ASSESSMENT OF PROPOSED CHANGES

My overall evaluation of the Applicant's proposed changes is provided here, categorized as changes for which we could rely upon evidenced-based support, and as regulatory decisions that are not based on review of data.

Evidence-based Changes:

1. **Change to Mifeprex and misoprostol doses, change in the dosing regimen, including misoprostol route of administration from oral to buccal and change in dosing interval between Mifeprex and misoprostol and the place in which the woman may take misoprostol**

Numerous studies evaluated the proposed doses of Mifeprex and misoprostol and the buccal route of administration for misoprostol, including in gestations through 70 days. The studies support that this revised regimen is safe and effective. (b) (4) [redacted]. It is important to note, however, that removal of the current regimen from labeling does not reflect any concerns about the safety or efficacy of that regimen.

There is a substantial body of literature assessing the dosing interval between Mifeprex and misoprostol; while it appears that intervals < 24 hours may be associated with a higher failure rate, the revised window of 24-48 hours after Mifeprex in which misoprostol may be taken maintains an acceptable level of safety and efficacy of the regimen.

A large number of the studies reviewed allowed for home administration of misoprostol, and a systematic review of studies including over 45,000 women, half of which incorporated home use of misoprostol, found very similar rates of treatment success and of ongoing pregnancy regardless of whether misoprostol was taken in-clinic or at home. Therefore, 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 location when the process begins.

2. **Inclusion of an option to administer a second dose of misoprostol to women who do not have a complete expulsion of the pregnancy at follow-up**

Many studies included in the treatment regimen the option for a second dose of misoprostol for women who had not completed the expulsion of the products of conception by follow-up, and some specifically evaluated the success of a second dose. The available data support the safety and efficacy of a repeat dose of misoprostol if complete expulsion of the products of conception has not occurred but the pregnancy is not ongoing. The ability to offer this option may reduce the need for surgical intervention. While there is a suggestion that the success rate following a second dose of misoprostol may be somewhat lower at more advanced gestational ages, there is no evidence that the practice of offering an additional dose results in adverse effects.

Surgical evacuation of the uterus is still recommended in labeling in the case of an ongoing pregnancy.

3. Change in the gestational age through which the Mifeprex regimen has been found to be safe and effective for use

Of the studies that supported the proposed changes in the dosing regimen, four of them, including almost 3,000 women, evaluated the safety and effectiveness of the regimen in women through 70 days gestation. A number of additional studies supported safety and effectiveness of the regimen for gestations later than the currently labeled 49 days but < 64 days.

4. Change in timing and description of follow-up

A large systematic review supported the appropriateness of follow-up assessment being made as soon as 7 days through 14 days after Mifeprex administration.

A number of studies evaluated 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. The labeling will not be directive regarding specific details of how follow-up will be performed; that will be a decision made between the healthcare provider and patient.

5. Change in who may be a certified provider

The Applicant noted that the training and qualification of who can perform medical abortion is regulated on the state level, with 15 states having laws that specifically permit non-physician providers (such as nurse practitioners, physician assistants and certified nurse-midwives) to provide medical abortion. Studies that evaluated the proposed dosing regimen given by non-physicians demonstrated continued high rates of success at gestational ages through 70 days, as compared to care provided by physicians. The data on use by non-physician healthcare providers, therefore, support that it is safe and effective to permit healthcare providers who are licensed to prescribe medications to prescribe and administer Mifeprex, provided they meet the requirements for certification described in the REMS.

6. Change in labeling describing the time to expulsion of products of conception

Data were reviewed that support the revised description of the time interval during which expulsion of the products of conception typically occurs as 2-24 hours. Providing accurate information in labeling will aid the woman in ensuring she is in an appropriate setting when expulsion is likely to occur.

Regulatory Changes:

1. Addition of misoprostol to the indication statement in the Indication and Use section of labeling

Inclusion of misoprostol in the indication statement is appropriate because all the data reviewed for this supplement and for the original Mifeprex application was based on a treatment regimen that included both drugs. Current FDA labeling practice is to include information in the indication statement if the labeled drug is to be used only in conjunction with another therapy.

2. Removal of the term "under Federal law" from two sections of the Prescriber's Agreement

The Division and (b) (6) were unable determine a rationale for the inclusion of this phrase. The phrase appears redundant, because all of the requirements under the REMS are imposed

as a matter of Federal law. There is no precedent for this terminology in other REMS documents; therefore, it should be removed.

9. Advisory Committee Meeting

The original application for Mifeprex was the subject of a meeting of the Reproductive Health Drugs Advisory Committee in July 1996, which resulted in a vote of 6-0 (with 2 abstentions) that the benefits outweighed the risk for this product. An Advisory Committee meeting was not requested for this efficacy supplement because there were no complex scientific or other issues on which input from outside experts was needed.

10. Pediatrics

This application trigged PREA because it addresses a new dosing regimen. The Applicant requested a waiver of pediatric studies in females < 12 years of age because the indication is not relevant to this premenarcheal population. The Applicant stated that safety and efficacy data are available for over 300 adolescent patients aged 12 to 16 years. As discussed in the primary review, Gatter[12] included data on 322 adolescents from 11 through 16 years old (106 of whom were under 16 years) and on 283 17 year olds, which demonstrated efficacy similar to (even numerically greater than) that of the entire study population. No pediatric cases required transfusion, hospitalization or treatment for severe infection. Upadhyay[36] looked at abortion-related complications by age, with the lowest category being ≤ 19 years and found no statistical difference and a nominally lower rate for the younger females compared to women aged 20-24 years; however, this included both medical and surgical abortions.

(b) (6), (b) (4)

The Applicant did not have specific data on adherence in any age group, but stated that the equivalent levels of efficacy for females < 17 years compared to females ≥ 17 years indicates that there is no clinically significant difference in adherence by age. As for follow-up, the Applicant provided information from four studies (Gatter[12], Cameron[40, 41], Ngoc[42], Horning[43]), which included a total of 346 females < 17 years, with most of the data coming from Gatter. For the females < 17 years, adherence to follow-up ranged from 78-100%, and averaged 78.6%, while for females ≥ 17 years, adherence ranged from 77-96%, and averaged

[40] Cameron ST, Glasier A, Dewarta H, Johnstone A, Burnside A. Telephone follow-up and self-performed urine pregnancy testing after early medical abortion: a service evaluation. Contraception 2012; 86: 67-73

[41] 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

[42] 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

[43] 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

85.1%. Thus, it does not appear that there is any meaningful difference based on age in a postmenarcheal female's ability to comply with the dosing regimen and follow-up.

(b) (6) agreed to a partial waiver for patients from birth to 11 years of age, and concurred that adequate data are available for postmenarchal adolescents.

11. Other Relevant Regulatory Issues

Because this efficacy supplement is based on published literature, no consult was made to the (b) (6)

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 and 14. 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 US vs. non-US study location revealed that there were large differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the US studies. This may reflect differences in ascertainment or subject reporting of adverse reactions in non-US studies. Regardless, inclusion of this non-US data would not be appropriate, as it is unlikely to be informative to the US 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.

13. Recommendations/Risk Benefit Assessment

13.1 RECOMMENDED REGULATORY ACTION

I recommend that the Mifeprex efficacy supplement receive an Approval action.

13.2 RISK BENEFIT ASSESSMENT

The data reviewed in support of the changes proposed in this efficacy supplement confirm that the Mifeprex regimen as revised is safe and effective for termination of intrauterine pregnancy through 70 days gestation; for this reason, I believe that the benefit/risk profile of Mifeprex is favorable. (b) (6) and (b) (6) continue to recommend a REMS for this product, but agree that the experience over the past 16 years demonstrates that certain elements of the REMS may be modified or eliminated, as detailed below.

13.3 RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES

I concur with the changes to the REMS program described in Section 8.6.1, which include:

- Provision for "healthcare providers who prescribe" who meet the qualifications specified in the REMS to become certified and thereby allowed to order, prescribe and administer Mifeprex
- Revision of the Prescriber's Agreement (now called the Prescriber's Agreement Form) to reflect labeling revisions pursuant to this efficacy supplement
- Removal of the Patient Agreement from the REMS
- Removal of the Medication Guide from the REMS
- Revision of the provider reporting requirements to require reporting only of deaths to the Applicant
- Removal of the term "under Federal law" from the Prescriber's Agreement

13.4 RECOMMENDATION FOR OTHER POSTMARKETING STUDY REQUIREMENTS AND COMMITMENTS

I concur with (b) (6) that no postmarketing study requirements or commitments are warranted.

13.5 RECOMMENDED COMMENTS TO APPLICANT

None

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Appendix 1

Table 4 Summary Table of Studies Supporting NDA 20-687, Supplement 020

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other endi
Revision of Dosing Regimen (doses, ROA, dosing interval)								
Winikoff 2012 US	OL prospective trial	729 (56-63 days: 379 64-70 days: 350)	57-70 days	2nd dose of miso allowed for incomplete Ab		Regimen, *Home miso, GA*	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: Hospitalizatio 0.6% Sepsis 0.2% Common AEs reported
Boersma 2011 Curacao	Prospective observational	330	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1st dose		Regimen, *GA*	Total: 97.7% ≤ 49: 97.8% 50-63: 93.7% 64-70: 96.2% Total ongoing preg: 0.7%	Hospitalizatio
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		Regimen, *Other HCPs*	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD g hosp for bleed underwent SA No transfusio Hospitalizatio
Sanhueza Smith 2015 Mexico	Observational	1,001 (≤ 56 days: 622 57-63 days: 196 64-70 days:	70 days			Regimen, GA	≤ 56: 94.9% 57-63: 90.0% 64-70: 91.2% Success in ≤ 56 arm signif > in 57-63 arm	Serious AEs r described

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
		151)						
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		Regimen	Total: 96.6%	Infection 0.01 Transfusions 0.6% Hospitalizatio 0.9% Buccal vs. ora ↓nausea, dia fever, dizzines
						GA	*≤49: 98.1%* *50-56: 96.7%* *57-63: 95.2%* *64-70: 93.1%*	
						Dose interval	Overall: 24 hr: 94.2% 24-48 hr: 96.8% ≤49 days: 24 hr: 96.8% 24-48 hr: 98.2% 50-63 days: 24 hr: 92.1% 24-48 hr: 96.3% All comparisons sig different	
						2nd dose miso	*91-100% success*	
Chong 2015 US	Prospective, non-randomized, OL study	400 (128 took Mife at home; 272 in clinic)	63 days			Regimen	Clinic use: 96.9% Home use: 96.3% NS different	Hospitalizatio AEs NR
Gatter 2015 US	Observational	13,373	63 days			Regimen, *GA, Adolescents*	Total: 97.7% 22-28: 97.3% 29-35: 98.8%	Odds of medi aspiration ↑ at higher GA

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
							36-42: 98..8% 43-49: 98.1% 50-56: 96.9% 57-63: 95.5% Total ongoing preg: 0.5%	Infx req'g hospitalizatio 0.01% Total hospital 0.04% Transfusion 0
Grossman, Grindley et al. 2011 US	Prospective cohort	578 (281 telemedicine, 297 face-to-face)	63 days			Home miso	Face-to-face group: 96.9% Telemed group: 98.7%	No deaths or hospitalizatio transfusion 0.
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2nd dose of miso allowed for incomplete Ab		Regimen, MAB vs. SAB *(additional dose, home miso)*	MAB 99.6% SAB 99.8%	Hospitalizatio visit, uterine perforation, infection, transfusion – in total, NS di
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	Regimen, *home miso*	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm	Common AEs reported Fever/chills m frequent with
						GA	*Buccal:* *≤ 42: 98.7%* *43-49: 96.4%* *50-56: 95.7%* *57-63: 94.8%*	
Alam 2013 Bangladesh	Prospective study of menstrual regulation	651	63 days			Regimen	93% (in 606 women with documented	Common ARs reported

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
							pregnancy at tx)	
Blum, Raghavan et al. 2012 Tunesia & Vietnam	DB RCT, placebo control	441 (220 mife/miso, 221 miso only)	63 days			Regimen, *home miso*	Total: 92.9%	Serious AEs r discussed
						GA	*≤ 49: 96.3%* *50-56: 86.5%* *57-63: 96.3%*	
Chai 2013 Hong Kong	DB RCT	90 (45 in each arm)	63 days			Regimen: Buccal vs. SL miso	Buccal: 95.4% SL: 97.8% NS different Both ROAs had 100% success in GA ≤ 49 days	AEs similar ex chills sig high SL arm
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		Regimen	Total: 96.4% (Either dose)	↑ AEs in 800 a Vomiting 22% Fever/chills 3
						GA	*≤ 42: 95.8%* *43-49: 96.2%* *50-56: 98.5%* *57-63: 93.0%*	
						2nd dose of miso	*92% success*	
Giri 2011 Nepal	Prospective	100	63 days			Regimen	Total 93.6%	No transfusio hospitalizatio
Goldstone 2012 Australia	Retro observational	13,345	63 days			Regimen, *home miso*	96.5% Ongoing preg: 0.6%	1 death from s (<0.01%) Infection w/o s 0.2% Hemorrhage 0 Transfusion 0
Louie 2014 Azerbaijan	Observational	863	63 days			Regimen, Home miso	92% selected home misoprostol; overall success	Common AEs reported

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
							97%	
						GA	*Total: 97%* *≤ 49: 97%* *50-56: 99%* *57-63: 96%*	
Ngo 2012 Vietnam	Retrospective	337 (167 on proposed regimen)	63 days	Additional 200 mcg miso dose given if no bleeding by 3 hours post-miso; dose repeated again if no bleeding 2 hours later		Regimen: proposed vs. "Chinese regimen" of 150 mg Mife over 2 days, 600 mcg miso on Day 3	Proposed: 91.0% Chinese: 77.7% Add'l miso dose needed (1 dose): Proposed: 7.8% Chinese: 21.8% Add'l miso dose needed (2 doses): Proposed: 0% Chinese: 2.9%	AEs NR
Ngoc 2014 Vietnam	RCT	1,433 (713 to phone f/u; 720 to clinic f/u)	63 days			Regimen, *follow-up*	Phone arm: 94.8% Clinic arm: 94.6%	
Ngoc 2011 Vietnam	RCT	400 (Mife + miso: 202, miso-alone: 198)	63 days			Proposed regimen vs. miso-alone (home miso for both)	Proposed regimen: 96.5%	
		Proposed regimen by GA:				GA	Proposed regimen:	

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
		≤ 49: 162 50-56: 28 57-63: 11					≤ 49: 97.5% 50-56: 89.3% 57-63: 100%	
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551 50-56: 247 57-63: 171)	63 days	2nd dose of miso offered for incomplete Ab		Regimen, home miso	97.3%	Common AEs reported
						GA	*≤49: 98.0%* *50-56: 96.8%* *57-63: 95.9%*	
Creinin 2007 US	RCT	1,128	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: miso WITH Mife or 24 hrs later	Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2nd miso dose)	Higher rates o nausea, diarrh warmth/chills immediate mis SAEs: transfu 0.4% (all in 24 group); acute infx, treated a 0.9% (equally each group)
		With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145				*GA*	*24-hr interval; only a single miso dose:* *≤ 49: 94.3%* *50-56: 93.0%* *57-63: 94.5%* *(NS trend)*	
Creinin 2004 US	RCT	1,080	63 days	Add'l dose of miso if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: 6-8 hrs vs. 23-25 hrs after Mife	6-8 hrs vs. 1 day: NS diff 6-8 hr: 95.8% 1 day: 98.1% (incl Ss who got a 2nd miso dose)	Side effects d the interval b/ and miso were higher in the 2 hr group; rate nausea & vom after miso dos were also sig. in the 23-25 hr
		N in 24-hr interval arm by GA:				*GA*	*24-hr interval (1 or more miso doses):*	

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
		≤ 49: 258 50-56: 157 57-63: 116					*≤ 49: 98.4%* *50-56: 97.5%* *57-63: 98.3%*	group. Transfusion 0 (equal across Hosp for PID (only in 63 hr group)
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273) Buccal by GA: ≤ 49: 226 50-63: 38	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	Regimen (ROA) *GA*	Buccal: 97.1% *Buccal:* *≤ 49: 96.6%* *50-63: 100%*	No hospitaliza Common AEs reported
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		Regimen	Total: 95.2%; 1.1% ongoing preg Miso ≥ 800 mcg buccal: 96.8%; 0.7% ongoing preg	Hospitalizatio 0.3% Transfusion:
Wedisinghe 2010 US (4) UK (1)	Literature review (5 RCTs)	5,139	49-63 days	1 of 5 studies (N=49) used 600 mife + 400 oral miso	Vaginal miso	Dose interval	Pooled analysis: risk of failure for 0-24 hr vs. 24-72 hrs: 1.054 NS Trend for lower success if < 8 hour interval	NR

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
Fjerstad, Sivin et al 2009 US	Retrospective	1,638 (1,349 for proposed regimen; 334 oral miso)	59 days			Proposed regimen vs. oral miso in subset ≤ 49 days (both miso doses taken at home)	Proposed regimen: 98.3% Oral miso: 96.8%	
						Proposed regimen by GA	*28-34 days: 99.3%* *35-41: 98.8%* *42-48: 98.1%* *49-55: 98.3%* *56-59: 95.7%*	
Middleton 2005 US	OL RCT	442 (buccal 223, vaginal 219)	56 days			Regimen (buccal vs. vaginal miso)	Buccal: 95% Vaginal: 93% NS different Ongoing preg: Buccal: 0.9% Vaginal: 1.9%)	Transfusion 0 (buccal); Endometritis (all vaginal mi Similar rates common AEs diarrhea sig. r common with
Dahiya 2012 India	RCT	100 (miso + mife: 50, miso alone 50)	56 days			Proposed regimen vs. miso alone	Proposed regimen: 92%; no missed Ab or continued preg	
Kulier 2011 Global	Cochrane systematic review of RCTs (58 studies; 4 comparing mife dose)			200 vs. 600 mg mife;	Oral, vaginal, SL, buccal miso	Dose regimen	Mife 200 mg as effective as 600 mg; oral miso less effective than vaginal; SL & buccal miso as effective as vaginal but ↑	

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
							AEs	
Home Dosing of Misoprostol								
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at 64-70 days)	57-70 days	2nd dose of miso allowed for incomplete Ab		*Regimen,* Home miso, *GA*	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: Hospitalizatio 0.6% Sepsis 0.2% Common AEs reported
Abbas 2015 – Global	Literature review (6 studies, 4 using 800 mcg buccal miso)	For 800 mcg buccal miso: 781 at 57-63 days, 480 at 64-70 days)	70 days	400 mcg (& 800 mcg)	Vaginal & SL (& buccal) miso	*GA,* Home miso	Total over 4 studies of 800 buccal: 57-63: 93.5% 64-70: 92.5%	
Grossman, Grindley et al. 2011 US	Prospective cohort	578 (281 telemedicine, 297 face-to-face)	63 days			Home miso	Face-to-face group: 96.9% Telemed group: 98.7%	No deaths or hospitalizatio transfusion 0.
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2nd dose of miso allowed for incomplete Ab		*Regimen, MAB vs. SAB (additional dose,* home miso)	MAB 99.6% SAB 99.8%	Hospitalizatio visit, uterine perforation, infection, transfusion – in total, NS di
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	*Regimen,* home miso	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm	Common AEs reported Fever/chills m frequent with

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
						GA	***Buccal:*** ***≤ 42: 98.7%*** ***43-49: 96.4%*** ***50-56: 95.7%*** ***57-63: 94.8%***	
Blum, Raghavan et al. 2012 Tunesia & Vietnam	**DB RCT, placebo control**	**441 (220 mife/miso, 221 miso only)**	**63 days**			**Regimen, home miso**	**Total: 92.9%**	**Serious AEs r discussed**
						GA	***≤ 49: 96.3%*** ***50-56: 86.5%*** ***57-63: 96.3%***	
Chong 2012 Rep. of Georgia, Vietnam	**DB RCT**	**1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)**	**63 days**	400 vs. **800 mcg miso, 36-48 hours**		**Regimen (included option for home miso)**	**Total: 96.4% (Either dose)**	**↑ AEs in 800 a Vomiting 22% Fever/chills 3**
						GA	***800 mcg dose:*** ***≤ 42: 95.8%*** ***43-49: 96.2%*** ***50-56: 98.5%*** ***57-63: 93.0%***	
						2nd dose of miso	***2nd dose (all GA, both miso dose arms):*** ***92% success*** ***N unspecified***	
Goldstone 2012 Australia	**Retro observational**	**13,345**	**63 days**			***Regimen,* home miso**	**96.5%**	**Transfusion 0 1 death from s (<0.01%) Infection w/o s**

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
								Hemorrhage 0
Louie 2014 Azerbaijan	Observational	863	63 days			Home miso	92% selected home misoprostol; overall success 97%	Common AEs reported
						GA	Total: 97% *≤ 49: 97%* *50-56: 99%* *57-63: 96%*	
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551 50-56: 247 57-63: 171)	63 days	2nd dose of miso offered for incomplete Ab		Regimen, home miso	Total: 97.3% 94.9% with single miso dose	Common AEs reported
						GA	*≤49: 98.0%* *50-56: 96.8%* *57-63: 95.9%*	
Creinin 2007 US	RCT	1,128 (immediate miso: 567; 24 hours later at home: 561)	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	*Dose interval: miso WITH Mife or 24 hrs later at home*; home use	Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2nd miso dose)	Higher rates o nausea, diarrh warmth/chills immediate mis SAEs: transfu 0.4% (all in 24 group); acute infx, treated a 0.9% (equally each group)
		With 24-hr interval by GA:				*GA*	*24-hr interval; only a single miso dose:*	

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
		≤ 49: 229 50-56: 172 57-63: 145					*≤ 49: 94.3%* *50-56: 93.0%* *57-63: 94.5%* *(NS trend)*	
Swica 2013 US	Observational	301 (139 chose home mife; 162 chose clinic mife)	63 days	6-48 hour dose interval	RoA for miso not specified	Home miso	Clinic use of mife: 95.6% Home use of mife: 96.7% NS different	1 hospitalizati other SAEs Common AEs
Kopp Kallner 2010 Sweden	Prospective observational	395 (203 < 50 d; 192 50-63 d)	63 days		Vaginal miso	Home miso, *GA*	< 50: 98% 50-63: 96.9%	No SAEs, transfusions serious infx
Lokeland 2014 Norway	Prospective observational	1,018	63 days		Vaginal miso	Home miso, *GA*	Success + no unplanned visits: 93.6% (no data by GA)	Surgery: < 49: 4.1% 49-55: 3.2% 56-63: 8.1% Transfusion 0 Aspiration for bleeding 8%
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		*Regimen* Home miso (in-clinic administration required or not)	Failure rate: In-clinic - Yes: 5.2% No: 4.5% Ongoing pregnancy: In-clinic - Yes: 1.0% No: 1.2% No evidence of	Hospitalizatio 0.3% Transfusion:

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
							higher failure rate in logistic regression model if in-clinic admin was not required	
Additional Dose of Misoprostol								
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at 64-70 days)	57-70 days	2nd dose of miso allowed for incomplete Ab		*Regimen, Home miso, GA*	*57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA*	Transfusion: Hospitalizatio 0.6% Sepsis 0.2% Common AEs reported
						2nd dose of miso	57-63: 91% (N=11) 64-70: 66.7% (N=9)	
Boersma 2011 Curacao	Prospective observational	330	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1st dose		*Regimen,* 2nd dose of miso	2nd dose: 80% success (N=5)	
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		2nd dose miso	2nd dose: 91-100% success	Infection 0.01- Transfusions 0.6% Hospitalizatio 0.9% Buccal vs. ora ↓nausea, ↓dia fever, dizzines
Bracken 2014	Prospective comparative	703 (389 at 57-63	70 days	400 mcg miso	SL miso	*GA*	*57-63: 94.8%64-70: 91.9%*	2nd dose of mi bleeding or

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
Ukraine, Rep. of Georgia, India, Tunisia	OL	days, 325 at 64-70 days)				2nd dose of miso	2nd dose: 57-63: 90.9% (N=22) 64-70: 86.3% (N=34)	incomplete M 57-63: 5.7% 64-70: 10.9% Surgery for excessive pro bleeding: 57-63: 0.5% 64-70: 2.5% Hosp for blee 57-63: 0.5% 64-70: 0.3% Transfusion: 57-63: 0.3% 64-70: 0.3%
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	2nd dose of miso part of regimen	2nd dose: Buccal: 92.9% (N=14)	Common AEs reported: Fever/chills m frequent with
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		*Regimen*	*Total: 96.4% (Either dose)*	↑ AEs in 800 a Vomiting 22% Fever/chills 3
						GA	*800 mcg dose:* *≤ 42: 95.8%* *43-49: 96.2%* *50-56: 98.5%* *57-63: 93.0%*	
						2nd dose of miso	2nd dose (all GA, both miso dose arms):	

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
							92% success N unspecified	
Louie 2014 Azerbaijan	Observational	863	63 days			*Home miso*	*92% selected home misoprostol; overall success 97%*	Common AEs reported
Reeves 2008 US	Pooled secondary analysis of 2 RCTs	1,972	63 days		Vaginal miso	2nd dose miso	2nd dose: 62% success N=68	
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273)	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	*Regimen (ROA)*	*Buccal: 97.1%*	No hospitaliza Common AEs reported
		Buccal by GA: ≤ 49: 226 50-63: 38				*GA*	Buccal: *≤ 49: 96.6%* *50-63: 100%*	
						2nd dose of miso	100% (N=2, both in buccal arm)	
Coyaji 2007 India	RCT, placebo control	300 (150 in each arm)	56 days	400 mcg miso vs. 2 doses 400 mcg w/in 3 hours	Oral miso	2nd dose of miso	1 dose: 86% 2 doses: 92% Contin'd preg: 1 dose: 7% 2 doses: 1%	Surg for bleed no difference
Increased Gestational Age								

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at 64-70 days)	57-70 days	2nd dose of miso allowed for incomplete Ab		*Regimen, Home miso,* GA	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: Hospitalizatio 0.6% Sepsis 0.2% Common AEs reported
Boersma 2011 Curacao	Prospective observational	330 (< 49: 199, 50-63: 105, 64-70: 26)	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1st dose		*Regimen,* GA	Total: 97.7% ≤ 49: 97.8% 50-63: 95.8% 64-70: 96.2%	
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		*Regimen, Other HCPs*	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD g hosp for bleed underwent SA No transfusio Hospitalizatio
Sanhueza Smith 2015 Mexico	Observational	1,001 (622 ≤ 56 days, 196 57-63 days, 151 64-70 days)	70 days			Regimen, GA	≤ 56: 94.9% 57-63: 90.0% 64-70: 91.2% Success in ≤ 56 arm signif > in 57-63 arm	Serious AEs r described
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		GA	Total: 96.6% ≤49: 98.1% 50-56: 96.7% 57-63: 95.2% 64-70: 93.1%	Infection 0.01 Transfusions 0.6% Hospitalizatio 0.9% Buccal vs ora ↓nausea, diar
						Dose interval	*24 hr: 94.2%* *24-48 hr: 96.8%*	

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
						2nd dose miso	*91-100% success*	fever, dizzines
Gouk 1999 UK	Prospective observational	253 (127 at 64-70 days)	63-83 days		Vaginal miso	GA	Overall: 94.5% 64-70: 94.5%	Common AEs reported
Bracken 2014 Ukraine, Rep. of Georgia, India, Tunisia	Prospective comparative OL	703 (389 at 57-63 days, 325 at 64-70 days)	70 days	400 mcg miso	SL miso	GA	57-63: 94.8%64-70: 91.9%	2nd dose of mi bleeding or incomplete MA 57-63: 5.7% 64-70: 10.5% Surgery for excessive/pro bleeding: 57-63: 0.5% 64-70: 2.5% Hosp for blee 57-63: 0.5% 64-70: 0.3% Transfusion: 57-63: 0.3% 64-70: 0.3%
Abbas 2015 – Global	Literature review (6 studies, 4 using 800 mcg buccal miso)	For 800 mcg buccal miso: 781 at 57-63 days, 480 at 46-70 days)	70 days	400 mcg (& 800 mcg)	Vaginal & SL (& buccal) miso	GA, *home miso*	Total over 4 studies of 800 buccal: 57-63: 93.5% 64-70: 92.5%	
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal,	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	*Regimen, home miso*	*Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal*	Common AEs reported, Fever/chills m frequent with

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
		426 oral)					*arm*	
Blum, Raghavan et al. 2012 Tunesia & Vietnam	DB RCT, placebo control	441 (220 mife/miso, 221 miso only)	63 days			*Regimen, home miso*	*Total: 92.9%*	Serious AEs r discussed
						GA	≤ 49: 96.3% 50-56: 86.5% 57-63: 96.3%	
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		*Regimen*	*Total: 96.4% (Either dose)*	↑ AEs in 800 a Vomiting 22% Fever/chills 3
						GA	≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%	
						2nd dose of miso	*92% success*	
Louie 2014 Azerbaijan	Observational	863	63 days			*Home miso (92%)*	92% selected home misoprostol; overall success 97%	Common AEs reported
						GA	≤ 49: 97% 50-56: 99% 57-63: 96%	
Ngoc 2011 Vietnam	RCT	400 (Mife + miso: 202, miso-alone: 198)	63 days			*Proposed regimen vs. miso-alone (home miso for both)*	*Proposed regimen: 96.5%*	
		Proposed regimen by GA: ≤ 49: 162 50-56: 28 57-63: 11				GA	Proposed regimen: ≤ 49: 97.5% 50-56: 89.3% 57-63: 100%	

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551 50-56: 247 57-63: 171)	63 days	2nd dose of miso offered for incomplete Ab		*Regimen, home miso*	*97.3%*	Common AEs reported
						GA	≤49: 98.0% 50-56: 96.8% 57-63: 95.9%	
Creinin 2007 US	RCT	1,128	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	*Dose interval: miso WITH Mife or 24 hrs later*	*Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2nd miso dose)*	Higher rates o nausea, diarrh warmth/chills immediate mis SAEs: transfu 0.4% (all in 24 group); acute infx, treated a 0.9% (equally each group)
		With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145				GA	24-hr interval; only a single miso dose: ≤ 49: 94.3% 50-56: 93.0% 57-63: 94.5% (NS trend)	
Creinin 2004 US	RCT	1,080	63 days	Add'l dose of miso if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	*Dose interval: 6-8 hrs vs. 23-25 hrs after Mife*	*6-8 hrs vs. 1 day: NS diff 6-8 hr: 95.8% 1 day: 98.1% (incl Ss who got a 2nd miso dose)*	Side effects c the interval b/ and miso were higher in the 2 hr group; rate nausea & vom after miso dos were also sig. in the 23-25 hr group. Transfusion 0 (equal across
		N in 24-hr interval arm by GA: ≤ 49: 258 50-56: 157 57-63: 116				GA	24-hr interval (1 or more miso doses): ≤ 49: 98.4% 50-56: 97.5% 57-63: 98.3%	

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
								Hosp for PID (only in 6-8 hr group)
Kopp Kallner 2010 Sweden	Prospective observational	395 (203 < 50 d; 192 50-63 d)	63 days		Vaginal miso	*Home miso, GA*	< 50: 98% 50-63: 96.9%	No SAEs, transfusions o serious infx
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273)	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	*Regimen (ROA)*	*Buccal: 97.1%*	No hospitaliza Common AEs reported
		Buccal by GA: ≤ 49: 226 50-63: 38				GA	Buccal: ≤ 49: 96.6% 50-63: 100%	
Fjerstad, Sivin et al 2009 US	Retrospective	1,638 (1,349 for proposed regimen; 334 oral miso)	59 days			*Proposed regimen vs. oral miso in subset ≤ 49 days (both miso doses taken at home)*	*Proposed regimen: 98.3%* *Oral miso: 96.8%*	
						Proposed regimen by GA	28-34 day: 99.3% 35-41: 98.8% 42-48: 98.1% 49-55: 98.3% 56-59: 95.7%	
Method of Follow-up								
Ngoc 2014 Vietnam	RCT	1,433 (713 to phone f/u; 720 to clinic f/u)	63 days			*Regimen*	*Phone arm: 94.8%* *Clinic arm: 94.6%*	
						Follow-up: phone + semi-quant UPT 2 weeks after Mife vs. in-clinic f/u		Phone f/u Sens: 92.8% Spec: 90.6% UPT alone:

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
								Sens: 95.7%
Perriera 2010 US	Prospective cohort	139	63 days		Buccal (N=6) or vaginal (N=127) miso	Follow-up: phone f/u @ 7 days + HSUP @ 30 days		Successful f/u 97.1% Prediction per phone f/u Sens: 95.9% Spec: 50% PPV: 97.5% NPV: 37.5% Transfusion 1 Hospitalizatio infx 0.7%
Blum, Shochet et al. 2012 US	Open-label trial	490	63 days	Not specified	Not specified	Follow-up: at-home semi-quant UPT vs. in-clinic	20% LTFU; 97.5% success;	Sens: 100% Spec: 97% PPV: 9.1% NPV: 100% Screen+: 9.1%
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		*Regimen*	*Total: 95.2%; 1.1% ongoing preg* *Miso ≥ 800 mcg buccal: 96.8%; 0.7% ongoing preg*	Hospitalizatio 0.3% Transfusion:
						Time of f/u	Logistic regression – no difference in	

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
							failure rate by time of f/u (< 1 week vs. ≥ 1 wk)	
Rossi 2004 US	Secondary analysis of RCT	1,080	63 days		Vaginal miso; 6-8 hr vs. 23-25 hr interval	Follow-up (pt assess vs. HCP assess vs. sono)		Pt: Sens 96.5% Spec 31.3% NPV 98.8% PPV 13.5%
Cameron 2015 Scotland	Retro database review	1,726	63 days		Vaginal miso	Follow-up (LSUP + sx + guidance on when to call clinic)	Ongoing preg: 0.5%	Unsched/eme visit: 2% (mai bleeding)
Cameron 2012 Scotland	Practice evaluation	616 (476 for phone, 140 for sono)	63 days		Vaginal miso	Follow-up (phone + LSUP vs. sono)		Phone: 87% contacted; 85% screen - screen + Sens 75% Spec 86% NPV 99.7% PPV 6%
Michie 2014 Scotland	Retrospective database review	943	63 days		Vaginal miso	Follow-up: phone call + home LSUP		Sens: 100% Spec: 88% PPV: 3.6% NPV: 100%
Oppegaard 2014 Austria, Scandinavia	RCT, non-inferiority	924 (466 clinic f/u; 458 self-assess)	63 days		Vaginal miso	Follow-up (clinic vs. at-home semi-quant hCG)		Pregs undete hCG: 0.7%; LTFU NS diffe
Lynd 2013 Vietnam	Observational	300	63 days	Unspecified	Unspecified	Follow-up (Home semi-quant UPT)		Sens: 100% Spec: 89.7% PPV: 27.5% NPV: 100%

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
								Screen+: 13.3
Fiala 2003 Austria	Observational	217	49 days	600 mg mife, 400 mcg miso; Add'l dose of miso if no bleeding w/in 3 hrs of 1st dose	Oral miso	Follow-up (sono vs. hCG) *2nd dose of miso*	Total: 98.2% *N=28* *Success rate not provided*	2 aspirations hemorrhage
Healthcare Provider								
Puri 2015 Nepal	Non-equivalent comparison	596 (307 in NM arm, 289 in "standard care" arm)	Not specified, but notes MAB is legal to 84 days			Other HCPs	Incomplete abortions: NM: 1.6% "Standard care": 2.4%	No SAEs
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		*Regimen, 2nd dose miso,* Other HCPs	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD g hosp for bleed underwent SA No transfusio Hospitalizatio
Kopp Kallner 2015 Sweden	RCT - equivalence	1,180 (481 CNM, 457 MD)	63 days			Other HCPs	CNM: 99% MD: 97.4%	No serious complications transfusions
Warriner 2011 Nepal	RCT - equivalence	1,104 (542 nurse/NM; 535 MD)	63 days		Vaginal miso	Other HCPs	Ongoing preg or incomplete MAB: Nurse: 2.6% MD: 3.7%	No hospitaliza or bleeding re transfusion
Adolescents								
Gatter 2015 US	Observational	13,373	63 days			*Regimen, GA*	*Total: 97.7%* *22-28: 97.3%* *29-35: 98.8%*	Odds of bleedi aspiration ↑ at higher GA

Study Location	Design	Overall N	GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findi
							36-42: 98..8% *43-49: 98.1%* *50-56: 96.9%* *57-63: 95.5%*	Infx req'g hospitalizatio 0.01% Total hospital 0.04% Transfusion 0
		By age: < 18: 605 18-24: 6,684 25-29: 3,317 30-34: 1,613 35-39: 855 40+: 299				Data on 322 females age 11-16 years and 283 age 17 years	Success by age: < 18: 98.7% 18-24: 98.1% 25-29: 97.5% 30-34: 96.5% 35-39: 97.0% 40+: 97.3%	
Phelps 2001 US	Prospective	28 (Age 14-17)	56 days		Vaginal miso	Adolescents	100%	Common AEs effects") repo "no AEs"
Niinimaki 2011 Finland	Population-based retro cohort	27,030 (3,024 adolescents)	20 weeks (85% ≤ 84 days)	Unspecified (Mife + a prostaglandin analog)	Unspecified	Adolescent AEs	Incomplete Ab 6.9% Surgical evacuation 10.7%	AE rates in adolescents ORs for: Hemorrhage 0 Incomplete Ab Surgical evac No deaths
Other Topics								
Upadhyay 2015 US	Retro cohort	11,319 (MAB)	63 days	Not specified	Not specified	AEs		Any abortion- complication: Major complic 0.31%

(C)NM = (certified) nurse-midwife; HSUP= high-sensitivity urine pregnancy test; LSUP= low-sensitivity urine pregnancy test; LTFU = lost to follow-up; MAB = medical abortion; NR = not reported; NS = non-significant; OL = open-label; PID = pelvic inflammatory disease; RCT = randomized controlled trial; RoA = route of administration; UPT = urine pregnancy test

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Table of Studies for 20-687

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Revision of Dosing Regimen (doses, ROA, dosing interval)									
Winikoff 2012 US	OL prospective trial	729 (56-63 days: 379 64-70 days: 350)	57-70 days	2nd dose of miso allowed for incomplete Ab		Regimen, *Home miso, GA*	57-63: 93.5% 64-70: 92.8% Ongoing preg 3% at each GA	Transfusion: 0.5% Hospitalization: 0.6% Sepsis 0.2% Common AEs reported	13-14% LTFU Data includes women w/repeat miso
Boersma 2011 Curacao	Prospective observational	330	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1st dose		Regimen, *GA*	Total: 97.7% ≤ 49: 97.8% 50-63: 93.7% 64-70: 96.2% Total ongoing preg: 0.7%	Hospitalization 0.7%	
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		Regimen, *Other HCPs*	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD group: hosp for bleeding, underwent SAB No transfusions Hospitalization 0.1%	
Sanhueza Smith 2015 Mexico	Observational	1,001 (≤ 56 days: 622 57-63 days: 196 64-70 days: 151)	70 days			Regimen, GA	≤ 56: 94.9% 57-63: 90.0% 64-70: 91.2% Success in ≤ 56 arm signif > in 57-63 arm	Serious AEs not described	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		Regimen	Total: 96.6%	Infection 0.01-0.5% Transfusions 0.03-0.6% Hospitalization 0.04-0.9% Buccal vs. oral: ↓nausea, ↑diarrhea, fever, dizziness	Majority of data from proposed regimen
						GA	*≤49: 98.1%* *50-56: 96.7%* *57-63: 95.2%* *64-70: 93.1%*		
						Dose interval	Overall: 24 hr: 94.2% 24-48 hr: 96.8% ≤49 days: 24 hr: 96.8% 24-48 hr: 98.2% 50-63 days: 24 hr: 92.1% 24-48 hr: 96.3% All comparisons sig different		
						2nd dose miso	*91-100% success*		
Chong 2015 US	Prospective, non-randomized, OL study	400 (128 took Mife at home; 272 in clinic)	63 days			Regimen	Clinic use: 96.9% Home use: 96.3% NS different	Hospitalization 0.6% AEs NR	Objective was studying home use of Mife
Gatter 2015 US	Observational	13,373	63 days			Regimen, *GA, Adolescents*	Total: 97.7% 22-28: 97.3% 29-35: 98.8% 36-42: 98..8% 43-49: 98.1% 50-56: 96.9%	Odds of needing aspiration ↑ at higher GA Infx req'g hospitalization 0.01%	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
							57-63: 95.5% Total ongoing preg: 0.5%	Total hospitalization 0.04% Transfusion 0.03%	
Grossman, Grindley et al. 2011 US	Prospective cohort	578 (281 telemedicine, 297 face-to-face)	63 days			Home miso	Face-to-face group: 96.9% Telemed group: 98.7%	No deaths or hospitalizations, transfusion 0.2%	21-24% LTFU
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2nd dose of miso allowed for incomplete Ab		Regimen, MAB vs. SAB *(additional dose, home miso)*	MAB 99.6% SAB 99.8%	Hospitalization, ED visit, uterine perforation, infection, transfusion – 0.1% in total, NS different	Not included in efficacy labeling
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	Regimen, *home miso*	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm	Common AEs reported; Fever/chills more frequent with buccal	9.5% LTFU
						GA	*Buccal:* *≤ 42: 98.7%* *43-49: 96.4%* *50-56: 95.7%* *57-63: 94.8%*		
Alam 2013 Bangladesh	Prospective study of menstrual regulation	651	63 days			Regimen	93% (in 606 women with documented pregnancy at tx)	Common ARs reported	
Blum, Raghavan et	DB RCT, placebo	441 (220	63 days			Regimen, *home miso*	Total: 92.9%	Serious AEs not discussed	
						GA	*≤ 49: 96.3%*		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
al. 2012 Tunesia & Vietnam	control	mife/miso, 221 miso only)					*50-56: 86.5%* *57-63: 96.3%*		
Chai 2013 Hong Kong	DB RCT	90 (45 in each arm)	63 days			Regimen: Buccal vs. SL miso	Buccal: 95.4% SL: 97.8% NS different Both ROAs had 100% success in GA ≤ 49 days	AEs similar except chills sig higher in SL arm	
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		Regimen	Total: 96.4% (Either dose)	↑ AEs in 800 arm: Vomiting 22% Fever/chills 33%	
						GA	*≤ 42: 95.8%* *43-49: 96.2%* *50-56: 98.5%* *57-63: 93.0%*		
						2nd dose of miso	*92% success*		
Giri 2011 Nepal	Prospective	100	63 days			Regimen	Total 93.6%	No transfusions or hospitalizations	
Goldstone 2012 Australia	Retro observational	13,345	63 days			Regimen, *home miso*	96.5% Ongoing preg: 0.6%	1 death from sepsis (<0.01%) Infection w/o sepsis 0.2% Hemorrhage 0.1% Transfusion 0.1%	
Louie 2014 Azerbaijan	Observational	863	63 days			Regimen, Home miso	92% selected home misoprostol; overall success 97%	Common AEs reported	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
						GA	***Total: 97%*** ***≤ 49: 97%*** ***50-56: 99%*** ***57-63: 96%***		
Ngo 2012 Vietnam	**Retrospective**	**337 (167 on proposed regimen)**	**63 days**	**Additional 200 mcg miso dose given if no bleeding by 3 hours post-miso; dose repeated again if no bleeding 2 hours later**		**Regimen: proposed vs. "Chinese regimen" of 150 mg Mife over 2 days, 600 mcg miso on Day 3**	**Proposed: 91.0%** **Chinese: 77.7%** **Add'l miso dose needed (1 dose):** **Proposed: 7.8%** **Chinese: 21.8%** **Add'l miso dose needed (2 doses):** **Proposed: 0%** **Chinese: 2.9%**	**AEs NR**	
Ngoc 2014 Vietnam	**RCT**	**1,433 (713 to phone f/u; 720 to clinic f/u)**	**63 days**			**Regimen, *follow-up***	**Phone arm: 94.8%** **Clinic arm: 94.6%**		**Ngoc 2014 Vietnam**
Ngoc 2011 Vietnam	**RCT**	**400 (Mife + miso: 202, miso-alone: 198)**	**63 days**			**Proposed regimen vs. miso-alone (home miso for both)**	**Proposed regimen: 96.5%**		
		Proposed regimen by GA: **≤ 49: 162** **50-56: 28** **57-63: 11**				**GA**	**Proposed regimen:** **≤ 49: 97.5%** **50-56: 89.3%** **57-63: 100%**		
Pena 2014	**OL**	**1,000**	**63 days**	**2nd dose of**		**Regimen, home miso**	**97.3%**	**Common AEs**	**94.9% with**

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Mexico	prospective cohort	(by GA: ≤49: 551 50-56: 247 57-63: 171)		miso offered for incomplete Ab		 *GA*	 *≤49: 98.0%* *50-56: 96.8%* *57-63: 95.9%*	reported	single miso dose
Creinin 2007 US	RCT	1,128	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: miso WITH Mife or 24 hrs later	Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2nd miso dose)	Higher rates of nausea, diarrhea, warmth/chills with immediate miso. SAEs: transfusion 0.4% (all in 24-hour group); acute pelvic infx, treated as outpt 0.9% (equally in each group)	Looking at only a single miso dose, success for immediate vs. 1 day was 91% vs. 94%; did not meet n-i criteria.
		With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145				*GA*	*24-hr interval; only a single miso dose:* *≤ 49: 94.3%* *50-56: 93.0%* *57-63: 94.5%* *(NS trend)*		
Creinin 2004 US	RCT	1,080	63 days	Add'l dose of miso if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	Dose interval: 6-8 hrs vs. 23-25 hrs after Mife	6-8 hrs vs. 1 day: NS diff 6-8 hr: 95.8% 1 day: 98.1% (incl Ss who got a 2nd miso dose)	Side effects during the interval b/w Mife and miso were sig. higher in the 23-25 hr group; rates of nausea & vomiting after miso dose were also sig. higher in the 23-25 hr group. Transfusion 0.2% (equal across arms); Hosp for PID 0.2% (only in 6-8 hr	Looking at only a single miso dose, success for 6-8 hr vs. 1 day was 94.9% vs. 97.2%
		N in 24-hr interval arm by GA: ≤ 49: 258 50-56: 157 57-63: 116				*GA*	*24-hr interval (1 or more miso doses):* *≤ 49: 98.4%* *50-56: 97.5%* *57-63: 98.3%*		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
								group)	
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273) Buccal by GA: ≤ 49: 226 50-63: 38	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	Regimen (ROA) *GA*	Buccal: 97.1% *Buccal:* *≤ 49: 96.6%* *50-63: 100%*	No hospitalizations Common AEs reported	
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		Regimen	Total: 95.2%; 1.1% ongoing preg Miso ≥ 800 mcg buccal: 96.8%; 0.7% ongoing preg	Hospitalization: 0.3% Transfusion: 0.1%	Risk factors for failure: GA > 56 days, interval < 23 hours, oral vs. other RoA, 400 mcg vs. higher doses
Wedisinghe 2010 US (4) UK (1)	Literature review (5 RCTs)	5,139	49-63 days	1 of 5 studies (N=49) used 600 mife + 400 oral miso	Vaginal miso	Dose interval	Pooled analysis: risk of failure for 0-24 hr vs. 24-72 hrs: 1.054 NS Trend for lower success if < 8 hour interval	NR	4 with proposed doses include Creinin 2004 & 2007, Guest 2007 & Schaff 2000
Fjerstad, Sivin et al 2009	Retrospective	1,638 (1,349 for proposed	59 days			Proposed regimen vs. oral miso in subset ≤ 49 days (both miso	Proposed regimen: 98.3% Oral miso: 96.8%		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
US		regimen; 334 oral miso)				doses taken at home) *Proposed regimen by GA*	*28-34 days: 99.3%* *35-41: 98.8%* *42-48: 98.1%* *49-55: 98.3%* *56-59: 95.7%*		
Middleton 2005 US	OL RCT	442 (buccal 223, vaginal 219)	56 days			Regimen (buccal vs. vaginal miso)	Buccal: 95% Vaginal: 93% NS different Ongoing preg: Buccal: 0.9% Vaginal: 1.9%)	Transfusion 0.5% (buccal); Endometritis 0.9% (all vaginal miso) Similar rates of common AEs except diarrhea sig. more common with buccal	
Dahiya 2012 India	RCT	100 (miso + mife: 50, miso alone 50)	56 days			Proposed regimen vs. miso alone	Proposed regimen: 92%; no missed Ab or continued preg		
Kulier 2011 Global	Cochrane systematic review of RCTs (58 studies; 4 comparing mife dose)			200 vs. 600 mg mife;	Oral, vaginal, SL, buccal miso	Dose regimen	Mife 200 mg as effective as 600 mg; oral miso less effective than vaginal; SL & buccal miso as effective as vaginal but ↑ AEs		
Home Dosing of Misoprostol									
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at	57-70 days	2nd dose of miso allowed for incomplete Ab		*Regimen,* Home miso, *GA*	57-63: 93.5% 64-70: 92.8% Ongoing preg	Transfusion: 0.5% Hospitalization: 0.6%	13-14% LTFU Data includes

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
		64-70 days)					3% at each GA	Sepsis 0.2% Common AEs reported	women w/repeat miso
Abbas 2015 – Global	Literature review (6 studies, 4 using 800 mcg buccal miso)	For 800 mcg buccal miso: 781 at 57-63 days, 480 at 64-70 days)	70 days	400 mcg (& 800 mcg)	Vaginal & SL (& buccal) miso	*GA,* Home miso	Total over 4 studies of 800 buccal: 57-63: 93.5% 64-70: 92.5%		Sanhueza Winkoff 2012 Boersma Pena
Grossman, Grindley et al. 2011 US	Prospective cohort	578 (281 telemedicine, 297 face-to-face)	63 days			Home miso	Face-to-face group: 96.9% Telemed group: 98.7%	No deaths or hospitalizations, transfusion 0.2%	21-24% LTFU
Ireland 2015 US	Retro cohort	30,146 (13,221 MAB; 16,925 SAB)	63 days	Option for home Mife (74%); 2nd dose of miso allowed for incomplete Ab		*Regimen, MAB vs. SAB* *(additional dose,* home miso)	MAB 99.6% SAB 99.8%	Hospitalization, ED visit, uterine perforation, infection, transfusion – 0.1% in total, NS different	
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	*Regimen,* home miso	Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm	Common AEs reported; Fever/chills more frequent with buccal	
						GA	*Buccal:* *≤ 42: 98.7%* *43-49: 96.4%* *50-56: 95.7%* *57-63: 94.8%*		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Blum, Raghavan et al. 2012 Tunesia & Vietnam	DB RCT, placebo control	441 (220 mife/miso, 221 miso only)	63 days			Regimen, home miso	Total: 92.9%	Serious AEs not discussed	
						GA	*≤ 49: 96.3%* *50-56: 86.5%* *57-63: 96.3%*		
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		Regimen (included option for home miso)	Total: 96.4% (Either dose)	↑ AEs in 800 arm: Vomiting 22% Fever/chills 33%	# of women opting for home miso not specified
						GA	*800 mcg dose:* *≤ 42: 95.8%* *43-49: 96.2%* *50-56: 98.5%* *57-63: 93.0%*		
						2nd dose of miso	*2nd dose (all GA, both miso dose arms):* *92% success* *N unspecified*		
Goldstone 2012 Australia	Retro observational	13,345	63 days			*Regimen,* home miso	96.5%	Transfusion 0.1% 1 death from sepsis (<0.01%) Infection w/o sepsis Hemorrhage 0.1%	
Louie 2014 Azerbaijan	Observational	863	63 days			Home miso	92% selected home misoprostol; overall success 97%	Common AEs reported	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
						GA	**Total: 97%** ***≤ 49: 97%*** ***50-56: 99%*** ***57-63: 96%***		
Pena 2014 Mexico	**OL prospective cohort**	**1,000 (by GA: ≤49: 551 50-56: 247 57-63: 171)**	**63 days**	**2nd dose of miso offered for incomplete Ab**		**Regimen, home miso**	**Total: 97.3% 94.9% with single miso dose**	**Common AEs reported**	
						GA	***≤49: 98.0%*** ***50-56: 96.8%*** ***57-63: 95.9%***		
Creinin 2007 US	**RCT**	**1,128 (immediate miso: 567; 24 hours later at home: 561)**	**63 days**	**Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife**	**Vaginal miso**	***Dose interval: miso WITH Mife or 24 hrs later at home*; home use**	**Interval - immediate vs. 1 day: statistically non-inferior immed: 95.1% 1 day: 96.9% (incl Ss who got a 2nd miso dose)**	**Higher rates of nausea, diarrhea, warmth/chills with immediate miso.** **SAEs: transfusion 0.4% (all in 24-hour group); acute pelvic infx, treated as outpt 0.9% (equally in each group)**	**Looking at only a single miso dose, success for immediate vs. 1 day was 91% vs. 94%; did not meet n-i criteria.**
		With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145				***GA***	***24-hr interval; only a single miso dose:*** ***≤ 49: 94.3%*** ***50-56: 93.0%*** ***57-63: 94.5%*** ***(NS trend)***		
Swica 2013 US	**Observational**	**301 (139 chose home mife; 162 chose**	**63 days**	**6-48 hour dose interval**	**RoA for miso not specified**	**Home miso**	**Clinic use of mife: 95.6% Home use of mife: 96.7%**	**1 hospitalization, no other SAEs Common AEs NR**	**Objective was studying home use**

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
		clinic mife)					NS different		of Mife
Kopp Kallner 2010 Sweden	Prospective observational	395 (203 < 50 d; 192 50-63 d)	63 days		Vaginal miso	Home miso, *GA*	< 50: 98% 50-63: 96.9%	No SAEs, transfusions or serious infx	
Lokeland 2014 Norway	Prospective observational	1,018	63 days		Vaginal miso	Home miso, *GA*	Success + no unplanned visits: 93.6% (no data by GA)	Surgery: < 49: 4.1% 49-55: 3.2% 56-63: 8.1% Transfusion 0.1%; Aspiration for bleeding 8%	
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		*Regimen* Home miso (in-clinic administration required or not)	Failure rate: In-clinic - Yes: 5.2% No: 4.5% Ongoing pregnancy: In-clinic - Yes: 1.0% No: 1.2% No evidence of higher failure rate in logistic regression model if in-clinic admin was not required	Hospitalization: 0.3% Transfusion: 0.1%	Risk factors for failure: GA > 56 days, interval < 23 hours, oral vs. other RoA, 400 mcg vs. higher doses

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Additional Dose of Misoprostol									
Winikoff 2012 US	OL prospective trial	729 (379 at 56-63 days, 350 at 64-70 days)	57-70 days	2nd dose of miso allowed for incomplete Ab		*Regimen, Home miso, GA*	*57-63: 93.5%* *64-70: 92.8%* *Ongoing preg 3% at each GA*	Transfusion: 0.5% Hospitalization: 0.6% Sepsis 0.2% Common AEs reported	13-14% LTFU Data includes women w/repeat miso
						2nd dose of miso	57-63: 91% (N=11) 64-70: 66.7% (N=9)		
Boersma 2011 Curacao	Prospective observational	330	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1st dose		*Regimen,* 2nd dose of miso	2nd dose: 80% success (N=5)		
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		2nd dose miso	2nd dose: 91-100% success	Infection 0.01-0.5% Transfusions 0.03-0.6% Hospitalization 0.04-0.9% Buccal vs. oral: ↓nausea, ↑diarrhea, fever, dizziness	Majority of data from proposed regimen
Bracken 2014	Prospective comparative	703 (389 at 57-63	70 days	400 mcg miso	SL miso	*GA*	*57-63: 94.8%64-70: 91.9%*	2nd dose of miso for bleeding or	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Ukraine, Rep. of Georgia, India, Tunisia	OL	days, 325 at 64-70 days)				2nd dose of miso	2nd dose: 57-63: 90.9% (N=22) 64-70: 86.3% (N=34)	incomplete MAB: 57-63: 5.7% 64-70: 10.5% Surgery for excessive/prolonged bleeding: 57-63: 0.5% 64-70: 2.5% Hosp for bleeding: 57-63: 0.5% 64-70: 0.3% Transfusion: 57-63: 0.3% 64-70: 0.3%	
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	2nd dose of miso part of regimen	2nd dose: Buccal: 92.9% (N=14)	Common AEs reported; Fever/chills more frequent with buccal	
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		*Regimen*	*Total: 96.4%* *(Either dose)*	↑ AEs in 800 arm: Vomiting 22% Fever/chills 33%	
						GA	*800 mcg dose:* *≤ 42: 95.8%* *43-49: 96.2%* *50-56: 98.5%* *57-63: 93.0%*		
						2nd dose of miso	2nd dose (all GA, both miso dose arms): 92% success		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
							N unspecified		
Louie 2014 Azerbaijan	Observational	863	63 days			*Home miso*	*92% selected home misoprostol; overall success 97%*	Common AEs reported	
Reeves 2008 US	Pooled secondary analysis of 2 RCTs	1,972	63 days		Vaginal miso	2nd dose miso	2nd dose: 62% success N=68		Creinin 2004 Creinin 2007 Did not evaluate 2nd dose in orig papers
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273)	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	*Regimen (ROA)*	*Buccal: 97.1%*	No hospitalizations Common AEs reported	
		Buccal by GA: ≤ 49: 226 50-63: 38				*GA*	Buccal: *≤ 49: 96.6%* *50-63: 100%*		
						2nd dose of miso	100% (N=2, both in buccal arm)		
Coyaji 2007 India	RCT, placebo control	300 (150 in each arm)	56 days	400 mcg miso vs. 2 doses 400 mcg w/in 3 hours	Oral miso	2nd dose of miso	1 dose: 86% 2 doses: 92% Contin'd preg: 1 dose: 7% 2 doses: 1%	Surg for bleeding – no difference	Limited relevance due to different regimen
Increased Gestational Age									
Winikoff 2012	OL prospective	729 (379 at 56-63	57-70 days	2nd dose of miso allowed		*Regimen, Home miso,* GA	57-63: 93.5% 64-70: 92.8%	Transfusion: 0.5% Hospitalization:	13-14% LTFU

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
US	trial	days, 350 at 64-70 days)		for incomplete Ab			Ongoing preg 3% at each GA	0.6% Sepsis 0.2% Common AEs reported	Data includes women w/repeat miso
Boersma 2011 Curacao	Prospective observational	330 (< 49: 199, 50-63: 105, 64-70: 26)	70 days	Add'l dose of miso if no bleeding w/in 48 hrs of 1st dose		*Regimen,* GA	Total: 97.7% ≤ 49: 97.8% 50-63: 95.8% 64-70: 96.2%		
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		*Regimen, Other HCPs*	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD group: hosp for bleeding, underwent SAB No transfusions Hospitalization 0.1%	
Sanhueza Smith 2015 Mexico	Observational	1,001 (622 ≤ 56 days, 196 57-63 days, 151 64-70 days)	70 days			Regimen, GA	≤ 56: 94.9% 57-63: 90.0% 64-70: 91.2% Success in ≤ 56 arm signif > in 57-63 arm	Serious AEs not described	
Chen & Creinin 2015 Global	Systematic review	33,846 (20 studies)	70 days	All but 1 study w/proposed		GA	Total: 96.6% ≤49: 98.1% 50-56: 96.7% 57-63: 95.2% 64-70: 93.1%	Infection 0.01-0.5% Transfusions 0.03-0.6% Hospitalization 0.04-0.9% Buccal vs. oral: ↓nausea, ↑diarrhea, fever, dizziness	Majority of data from proposed regimen
						Dose interval	*24 hr: 94.2%* *24-48 hr: 96.8%*		
						2nd dose miso	*91-100% success*		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Gouk 1999 UK	Prospective observational	253 (127 at 64-70 days)	63-83 days		Vaginal miso	GA	Overall: 94.5% 64-70: 94.5%	Common AEs reported	
Bracken 2014 Ukraine, Rep. of Georgia, India, Tunisia	Prospective comparative OL	703 (389 at 57-63 days, 325 at 64-70 days)	70 days	400 mcg miso	SL miso	GA	57-63: 94.8%64-70: 91.9%	2nd dose of miso for bleeding or incomplete MAB: 57-63: 5.7% 64-70: 10.5% Surgery for excessive/prolonged bleeding: 57-63: 0.5% 64-70: 2.5% Hosp for bleeding: 57-63: 0.5% 64-70: 0.3% Transfusion: 57-63: 0.3% 64-70: 0.3%	
Abbas 2015 – Global	Literature review (6 studies, 4 using 800 mcg buccal miso)	For 800 mcg buccal miso: 781 at 57-63 days, 480 at 46-70 days)	70 days	400 mcg (& 800 mcg)	Vaginal & SL (& buccal) miso	GA, *home miso*	Total over 4 studies of 800 buccal: 57-63: 93.5% 64-70: 92.5%		Sanhueza Winkoff 2012 Boersma Pena
Winikoff 2008 US	OL RCT	966 847 in efficacy analysis (421 buccal, 426 oral)	63 days	Add'l dose of miso allowed if incomplete Ab	Oral vs. buccal miso	*Regimen, home miso*	*Buccal: 96.2% Oral: 91.3%, sig different Ongoing preg in 1% of buccal arm*	Common AEs reported; Fever/chills more frequent with buccal	9.5% LTFU
Blum,	DB RCT,	441	63 days			*Regimen, home miso*	*Total: 92.9%*	Serious AEs not	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Raghavan et al. 2012 Tunesia & Vietnam	placebo control	(220 mife/miso, 221 miso only)				GA	≤ 49: 96.3% 50-56: 86.5% 57-63: 96.3%	discussed	
Chong 2012 Rep. of Georgia, Vietnam	DB RCT	1,112 (559 in 400 mcg miso arm, 563 in 800 mcg miso arm)	63 days	400 vs. 800 mcg miso, 36-48 hours		*Regimen*	*Total: 96.4% (Either dose)*	↑ AEs in 800 arm: Vomiting 22% Fever/chills 33%	
						GA	≤ 42: 95.8% 43-49: 96.2% 50-56: 98.5% 57-63: 93.0%		
						2nd dose of miso	*92% success*		
Louie 2014 Azerbaijan	Observational	863	63 days			*Home miso (92%)*	92% selected home misoprostol; overall success 97%	Common AEs reported	
						GA	≤ 49: 97% 50-56: 99% 57-63: 96%		
Ngoc 2011 Vietnam	RCT	400 (Mife + miso: 202, miso-alone: 198)	63 days			*Proposed regimen vs. miso-alone (home miso for both)*	*Proposed regimen: 96.5%*		
		Proposed regimen by GA: ≤ 49: 162 50-56: 28 57-63: 11				GA	Proposed regimen: ≤ 49: 97.5% 50-56: 89.3% 57-63: 100%		
Pena 2014 Mexico	OL prospective cohort	1,000 (by GA: ≤49: 551	63 days	2nd dose of miso offered for incomplete		*Regimen, home miso*	*97.3%*	Common AEs reported	94.9% with single miso dose
						GA	≤49: 98.0%		

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
		50-56: 247 57-63: 171)		Ab			50-56: 96.8% 57-63: 95.9%		
Creinin 2007 US	RCT	1,128	63 days	Add'l dose of miso allowed if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	*Dose interval: miso WITH Mife or 24 hrs later*	*Interval - immediate vs. 1 day: statistically non-inferior* *immed: 95.1%* *1 day: 96.9%* *(incl Ss who got a 2nd miso dose)*	Higher rates of nausea, diarrhea, warmth/chills with immediate miso. SAEs: transfusion 0.4% (all in 24-hour group); acute pelvic infx, treated as outpt 0.9% (equally in each group)	Looking at only a single miso dose, success for immediate vs. 1 day was 91% vs. 94%; did not meet n-i criteria.
		With 24-hr interval by GA: ≤ 49: 229 50-56: 172 57-63: 145				GA	24-hr interval; only a single miso dose: ≤ 49: 94.3% 50-56: 93.0% 57-63: 94.5% (NS trend)		
Creinin 2004 US	RCT	1,080	63 days	Add'l dose of miso if incomplete Ab at sono 6-8 days after Mife	Vaginal miso	*Dose interval: 6-8 hrs vs. 23-25 hrs after Mife*	*6-8 hrs vs. 1 day: NS diff* *6-8 hr: 95.8%* *1 day: 98.1%* *(incl Ss who got a 2nd miso dose)*	Side effects during the interval b/w Mife and miso were sig. higher in the 23-25 hr group; rates of nausea & vomiting after miso dose were also sig. higher in the 23-25 hr group. Transfusion 0.2% (equal across arms); Hosp for PID 0.2% (only in 6-8 hr group)	Looking at only a single miso dose, success for 6-8 hr vs. 1 day was 94.9% vs. 97.2%
		N in 24-hr interval arm by GA: ≤ 49: 258 50-56: 157 57-63: 116				GA	24-hr interval (1 or more miso doses): ≤ 49: 98.4% 50-56: 97.5% 57-63: 98.3%		
Kopp	Prospective	395	63 days		Vaginal	*Home miso,* GA	< 50: 98%	No SAEs,	

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Kallner 2010 Sweden	observational	(203 < 50 d; 192 50-63 d)			miso		50-63: 96.9%	transfusions or serious infx	
Raghavan 2011 Moldova	OL RCT	550 (buccal: 277, SL: 273)	63 days	400 mcg miso; additional dose allowed for incomplete Ab	Buccal vs. SL miso	*Regimen (ROA)*	*Buccal: 97.1%*	No hospitalizations Common AEs reported	
		Buccal by GA: ≤ 49: 226 50-63: 38				GA	Buccal: ≤ 49: 96.6% 50-63: 100%		
Fjerstad, Sivin et al 2009 US	Retrospective	1,638 (1,349 for proposed regimen; 334 oral miso)	59 days			*Proposed regimen vs. oral miso in subset ≤ 49 days (both miso doses taken at home)*	*Proposed regimen: 98.3% Oral miso: 96.8%*		
						Proposed regimen by GA	28-34 day: 99.3% 35-41: 98.8% 42-48: 98.1% 49-55: 98.3% 56-59: 95.7%		
Method of Follow-up									
Ngoc 2014 Vietnam	RCT	1,433 (713 to phone f/u; 720 to clinic f/u)	63 days			*Regimen*	*Phone arm: 94.8% Clinic arm: 94.6%*		
						Follow-up: phone + semi-quant UPT 2 weeks after Mife vs. in-clinic f/u		Phone f/u: Sens: 92.8% Spec: 90.6% UPT alone: Sens: 95.7%	
Perriera 2010 US	Prospective cohort	139	63 days		Buccal (N=6) or vaginal (N=127)	Follow-up: phone f/u @ 7 days + HSUP @ 30 days		Successful f/u: 97.1% Prediction per	ROA difference irrelevant b/c

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
					miso			phone f/u: Sens: 95.9% Spec: 50% PPV: 97.5% NPV: 37.5% Transfusion 1.4% Hospitalization for infx 0.7%	studying f/u
Blum, Shochet et al. 2012 US	Open-label trial	490	63 days	Not specified	Not specified	Follow-up: at-home semi-quant UPT vs. in-clinic	20% LTFU; 97.5% success;	Sens: 100% Spec: 97% PPV: 9.1% NPV: 100% Screen+: 3.1%	Blum, Shochet et al. 2012 US
Raymond 2013 Global	Systematic review (87 studies)	45,528 (6 trials with N=2,205 had miso ≥ 800 mcg buccal)	63 days	200 mg Mife, various miso doses, RoAs, intervals		*Regimen*	*Total: 95.2%; 1.1% ongoing preg* *Miso ≥ 800 mcg buccal: 96.8%; 0.7% ongoing preg*	Hospitalization: 0.3% Transfusion: 0.1%	Risk factors for failure: GA > 56 days, interval < 23 hours, oral vs. other RoA, 400 mcg vs. higher doses
						Time of f/u	Logistic regression – no difference in failure rate by time of f/u (< 1 week vs. ≥ 1 wk)		
Rossi 2004 US	Secondary analysis of RCT	1,080	63 days		Vaginal miso; 6-8 hr vs. 23-25 hr interval	Follow-up (pt assess vs. HCP assess vs. sono)		Pt: Sens 96.5% Spec 31.3% NPV 98.8%	Different ROA ok since f/u

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
								PPV 13.5%	
Cameron 2015 Scotland	Retro database review	1,726	63 days		Vaginal miso	Follow-up (LSUP + sx + guidance on when to call clinic)	Ongoing preg: 0.5%	Unsched/emerg visit: 2% (mainly for bleeding)	
Cameron 2012 Scotland	Practice evaluation	616 (476 for phone, 140 for sono)	63 days		Vaginal miso	Follow-up (phone + LSUP vs. sono)		Phone: 87% contacted; 85% screen - 15% screen + Sens 75% Spec 86% NPV 99.7% PPV 6%	
Michie 2014 Scotland	Retrospective database review	943	63 days		Vaginal miso	Follow-up: phone call + home LSUP		Sens: 100% Spec: 88% PPV: 3.6% NPV: 100%	
Oppegaard 2014 Austria, Scandinavia	RCT, non-inferiority	924 (466 clinic f/u; 458 self-assess)	63 days		Vaginal miso	Follow-up (clinic vs. at-home semi-quant hCG)		Pregs undetected by hCG: 0.7%; LTFU NS different	Different ROA ok since f/u
Lynd 2013 Vietnam	Observational	300	63 days	Unspecified	Unspecified	Follow-up (Home semi-quant UPT)		Sens: 100% Spec: 89.7% PPV: 27.5% NPV: 100% Screen+: 13.3%	Unspec regimen ok since relates to f/u
Fiala 2003 Austria	Observational	217	49 days	600 mg mife, 400 mcg miso; Add'l dose of miso if no bleeding w/in 3 hrs of 1st dose	Oral miso	Follow-up (sono vs. hCG) *2nd dose of miso*	Total: 98.2% *N=28 Success rate not provided*	2 aspirations for hemorrhage	
Healthcare Provider									

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
Puri 2015 Nepal	Non-equivalent comparison	596 (307 in NM arm, 289 in "standard care" arm)	Not specified, but notes MAB is legal to 84 days			Other HCPs	Incomplete abortions: NM: 1.6% "Standard care": 2.4%	No SAEs	
Olavarrieta 2015 Mexico	RCT – non-inferiority	884 (450 MD, 434 nurse)	70 days	Miso 24 hrs after mife; add'l 800 mcg allowed if ongoing preg at F/U		*Regimen, 2nd dose miso,* Other HCPs	Nurse: 97.9% MD: 98.4% (incl women taking add'l miso dose)	1 SAE in MD group: hosp for bleeding, underwent SAB No transfusions Hospitalization 0.1%	
Kopp Kallner 2015 Sweden	RCT - equivalence	1,180 (481 CNM, 457 MD)	63 days			Other HCPs	CNM: 99% MD: 97.4%	No serious complications or transfusions	
Warriner 2011 Nepal	RCT - equivalence	1,104 (542 nurse/NM; 535 MD)	63 days		Vaginal miso	Other HCPs	Ongoing preg or incomplete MAB: Nurse: 2.6% MD: 3.7%	No hospitalizations or bleeding req'g transfusion	
Adolescents									
Gatter 2015 US	Observational	13,373	63 days			*Regimen, GA*	*Total: 97.7%* *22-28: 97.3%* *29-35: 98.8%* *36-42: 98..8%* *43-49: 98.1%* *50-56: 96.9%* *57-63: 95.5%*	Odds of needing aspiration ↑ at higher GA Infx req'g hospitalization 0.01% Total hospitalization 0.04% Transfusion 0.03%	
		By age: < 18: 605 18-24: 6,684 25-29: 3,317				Data on 322 females age 11-16 years and 283 age 17 years	Success by age: < 18: 98.7% 18-24: 98.1% 25-29: 97.5%		Applicant obtained GA-stratified

Study Location	Design	Overall N	Highest GA	Dose(s) studied (if other than proposed)	RoA (if other than buccal miso)	Topic evaluated	MAB Success (no surgical procedure)	Other findings	Comments
		30-34: 1,613 35-39: 855 40+: 299					30-34: 96.5% 35-39: 97.0% 40+: 97.3%		data from authors
Phelps 2001 US	Prospective	28 (Age 14-17)	56 days		Vaginal miso	Adolescents	100%	Common AEs ("side effects") reported "no AEs"	
Niinimaki 2011 Finland	Population-based retro cohort	27,030 (3,024 adolescents)	20 weeks (85% ≤ 84 days)	Unspecified (Mife + a prostaglandin analog)	Unspecified	Adolescent AEs	Incomplete Ab 6.9% Surgical evacuation 10.7%	AE rates ↓ in adolescents ORs for: Hemorrhage 0.87 Incomplete Ab 0.69 Surgical evac 0.78 No deaths	
Other Topics									
Upadhyay 2015 US	Retro cohort	11,319 (MAB)	63 days	Not specified	Not specified	AEs		Any abortion-related complication: 5.19% Major complication 0.31%	Limited value since regimen not specified

(C)NM = (certified) nurse-midwife; HSUP= high-sensitivity urine pregnancy test; LSUP= low-sensitivity urine pregnancy test; LTFU = lost to follow-up; MAB = medical abortion; NR = not reported; NS = non-significant; OL = open-label; PID = pelvic inflammatory disease; RCT = randomized controlled trial; RoA = route of administration; UPT = urine pregnancy test

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04/06/2016

This table was inadvertently truncated when appended to my original CDTL review and is included here for completeness.

Exhibit J

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

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%.

[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

[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)

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.

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/s/

(b) (6)

03/29/2016

Exhibit K

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

DATE: March 28, 2016

FROM: Janet Woodcock, MD
Director, Center for Drug Evaluation and Research

THRU: (b) (6)

TO: (b) (6)

RE: NDA 020687, Supp 20

The currently approved REMS for Mifeprex contains a Patient Agreement Form required to be signed by both the patient and the prescriber. During the review of the REMS in connection with supplement 20 to NDA 020687 submitted by the sponsor, (b) (6) found that the information contained in the Patient Agreement Form is generally duplicative of information in the Medication Guide and of information and counseling provided to patients under standard informed consent practices for medical care and under professional practice guidelines. For the reasons further described in their reviews, the reviewers recommended that the Patient Agreement Form be removed from the REMS.

After being briefed on the planned changes to the NDA that the Center was considering, the Commissioner concluded that continuing the REMS requirement for a signed Patient Agreement Form would not interfere with access and would provide additional assurance that the patient is aware of the nature of the procedure, its risks, and the need for appropriate follow-up care. He requested that the Patient Agreement Form be retained as an element of the REMS.

Therefore, I have asked (b) (6) and (b) (6) to continue to include a Patient Agreement Form in the REMS for Mifeprex.

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/s/

(b) (6)

03/29/2016

adding to for the record

Exhibit L

Initial Shared System REMS approval: 04/2019
Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg
Progestin Antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
   a. To become specially certified to prescribe mifepristone, healthcare providers must:
      i. Review the Prescribing Information for mifepristone.
      ii. Complete a *Prescriber Agreement Form*. By signing[1] a *Prescriber Agreement Form*, prescribers agree that:
         1) They have the following qualifications:
            a) Ability to assess the duration of pregnancy accurately
            b) Ability to diagnose ectopic pregnancies
            c) 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
         2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
   b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
      i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
      ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form.*

[1] In this REMS, the terms "sign" and "signature" include electronic signatures.

iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.

iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.

v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

vi. If mifepristone will be dispensed by a certified pharmacy:

1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.

2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.

3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.

vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:

1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.

2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.

3) Ensure that healthcare providers under their supervision follow guidelines i.-v.

c. Mifepristone Sponsors must:

i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.

ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:

1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.

2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.

iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.

The following materials are part of the Mifepristone REMS Program:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
- *Prescriber Agreement Form for GenBioPro, Inc.*
- *Patient Agreement Form*

2. Pharmacies that dispense mifepristone must be specially certified

   a. To become specially certified to dispense mifepristone, pharmacies must:

      i. Be able to receive *Prescriber Agreement Forms* by email and fax.

      ii. Be able to ship mifepristone using a shipping service that provides tracking information.

      iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.

      iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:

         1) Review the Prescribing Information for mifepristone.

         2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:

            a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.

            b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.

            c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.

            d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.

            e) Track and verify receipt of each shipment of mifepristone.

            f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.

            g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.

            h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.

            i) Maintain records of *Prescriber Agreement Forms*.

            j) Maintain records of dispensing and shipping.

            k) Maintain records of all processes and procedures including compliance with those processes and procedures.

            l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.

            m) Train all relevant staff on the Mifepristone REMS Program requirements.

n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

b. Mifepristone Sponsors must:

i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.

ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.

i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
- *Pharmacy Agreement Form for GenBioPro, Inc.*

3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form.*

a. The patient must sign a *Patient Agreement Form* indicating that the patient has:

i. Received, read and been provided a copy of the *Patient Agreement Form*.

ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:

a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.

i. The distributors must put processes and procedures in place to:

1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.

2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.

3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.

4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.

5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.

ii. Put processes and procedures in place to maintain a distribution system that is secure,

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

iii. Train all relevant staff on the Mifepristone REMS Program requirements.

iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.

2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.

3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.

4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.

5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.

7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

Exhibit M

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX® (mifepristone) tablets, for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning.

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- **Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)**

MIFEPREX is only available through a restricted program called the MIFEPREX REMS Program (5.3).
Before prescribing MIFEPREX, inform the patient about these risks.
Ensure the patient knows whom to call and what to do if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort or general malaise 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 another healthcare provider who did not prescribe MIFEPREX, so that provider knows that she is undergoing a medical abortion. (5.1, 5.2)

----------RECENT MAJOR CHANGES----------

Boxed Warning	3/2016
Indications and Usage (1)	3/2016
Dosage and Administration, Dosing Regimen (2.1)	3/2016
Dosage and Administration, Post-treatment Assessment: Day 7 to 14 (2.3)	3/2016
Warnings and Precautions, MIFEPREX REMS Program (5.3)	3/2016
Warnings and Precautions, Ectopic Pregnancy (5.4)	3/2016

----------INDICATIONS AND USAGE----------

MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

----------DOSAGE AND ADMINISTRATION----------

- 200 mg MIFEPREX on Day 1, followed 24-48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

----------CONTRAINDICATIONS----------

- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

----------WARNINGS AND PRECAUTIONS----------

- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or www.earlyoptionpill.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 3/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

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 *[see Warnings and Precautions (5.1)]*.**
- **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 *[see Warnings and Precautions (5.2)]*.**

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 *[see Warnings and Precautions (5.3)]*.

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.

1 INDICATIONS AND USAGE

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

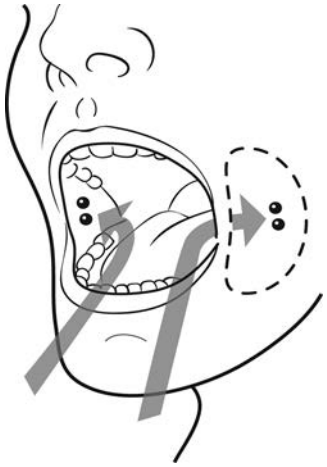
Remove any intrauterine device ("IUD") before treatment with MIFEPREX begins [*see Contraindications (4)*].

The dosing regimen for MIFEPREX and misoprostol is:

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
  - *Day One:* MIFEPREX Administration
    One 200 mg tablet of MIFEPREX is taken in a single oral dose.
  - *Day Two or Three:* Misoprostol Administration (minimum 24-hour interval between MIFEPREX and misoprostol)
    Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

    Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

    Figure 1



    2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol *[see Clinical Studies (14)]*, discuss with the patient an appropriate location for her to be when she takes the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms *[see Adverse Reactions (6)].*

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if she has questions following the administration of the misoprostol

- The name and phone number of the healthcare provider who will be handling emergencies.

2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

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 women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, women may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took Mifeprex and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Women who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion *[see Use in Specific Populations (8.1)]*. Advise the patient whether you will provide such care or will refer her to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with “MF.”

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the “treatment procedure”) is contraindicated in patients with any of the following conditions:
  - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) *[see Warnings and Precautions (5.4)]*
  - Chronic adrenal failure (risk of acute renal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute renal insufficiency)

- History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported *[see Adverse Reactions (6.2)]*)
- Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)
- Inherited porphyrias (risk of worsening or of precipitation of attacks)

- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device ("IUD") in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 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 *[see Boxed Warning]*. 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.

5.2 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 *[see Boxed Warning]*.

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 transfusions. 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 ≤ 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.

5.3 MIFEPREX REMS Program

MIFEPREX is available only through a restricted program under a REMS called the MIFEPREX REMS Program, because of the risks of serious complications *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the MIFEPREX REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form
- Patients must sign a Patient Agreement Form.
- 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

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies *[see Contraindications (4)].* 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.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis *[see Warnings and Precautions (5.1)]*
- Uterine bleeding *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from US studies, because rates reported in non-US studies were markedly lower and are not likely generalizable to the US population. In three US clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label.

Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most women can expect bleeding more heavily than they do during a heavy menstrual period *[see Warnings and Precautions (5.2)]*.

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# US 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

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-US Clinical Studies

Adverse Reaction	US			Non-US		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported
* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. 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.

Infections and infestations: post-abortal infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)
Blood and the lymphatic system disorders: anemia
Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)
Psychiatric disorders: anxiety
Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)
Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness
Respiratory, thoracic and mediastinal disorders: shortness of breath
Gastrointestinal disorders: dyspepsia
Musculoskeletal, connective tissue and bone disorders: back pain, leg pain
Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea
General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

regimen is unknown. Refer to the follow-up assessment *[see Dosage and Administration (2.3)]* to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Mifepristone is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant women are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant women with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone,fetal losses were much higher than in control animals. Skull deformaties were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

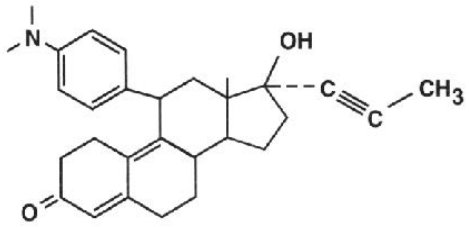
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for Cmax after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in women of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean Cmax was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean $AUC_{0-\infty}$ was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal) Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%

* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.
** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	<49 days			50-56 days			57-63 days			64-70 days		
	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

MIFEPREX is only available through a restricted program called the MIFEPREX REMS Program *[see Warnings and Precautions (5.3)].*

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with “MF.” Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [see Warnings and Precautions (5.2)].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [see Warnings and Precautions (5.1, 5.2)].
- MIFEPREX is only available through a restricted program called the MIFEPREX REMS Program [see Warnings and Precautions (5.3)]. Under the Mifeprex REMS Program:
    - Patients must sign a Patient Agreement Form.
    - MIFEPREX is only available in clinics, medical offices and hospitals and not through retail pharmacies.

Provider Contacts and Actions in Case of Complications

- 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, or if she experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever *[see Boxed Warning]*.
- Advise the patient to take the Medication Guide with her if she visits an emergency room or another healthcare provider who did not prescribe MIFEPREX, so that provider will be aware that the patient is undergoing a medical abortion with MIFEPREX.

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to14 days after taking MIFEPREX *[see Dosage and Administration (2.3)]*.
- Explain that
    - prolonged heavy vaginal bleeding is not proof of a complete abortion,
    - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
    - it is recommended that ongoing pregnancy be managed by surgical termination *[see Dosage and Administration (2.3)]*. Advise the patient whether you will provide such care or will refer her to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before she resumes sexual intercourse.

MIFEPREX is a registered trademark of Danco Laboratories, LLC.

Manufactured for:
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P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

3/2016

MEDICATION GUIDE

Mifeprex (MIF-eh-prex) (mifepristone) tablets, for oral use

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? 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. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.

Be sure to contact your healthcare provider promptly if you have any of the following:

- **Heavy Bleeding.** Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).
- **Abdominal Pain or "Feeling Sick."** If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
- **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.

If you cannot reach your healthcare provider, go to the nearest hospital emergency room. Take this Medication Guide with you. When you visit an emergency room or a healthcare provider who did not give you your Mifeprex, you should give them your Medication Guide so that they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.

Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.

What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
  Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider in a clinic, medical office, or hospital.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:

Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally

Day 1:

- Take 1 Mifeprex tablet by mouth.
- Your healthcare provider will either give you or prescribe for you 4 misoprostol tablets to take 24 to 48 hours later.

24 to 48 hours after taking Mifeprex:

- Place 2 misoprostol tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.

Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See "What is the most important information I should know about Mifeprex?"

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See "How should I take Mifeprex?" for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects.These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

Manufactured for: *Danco Laboratories, LLC*
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596) www.earlyoptionpill.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 3/2016

Exhibit N

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
REMS Modification

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
(b) (6)
(b) (6)

NDA: 020687
PRODUCT: Mifeprex (mifepristone) oral tablets
APPLICANT: Danco Laboratories (Danco)
FROM: (b) (6)
DATE: March 29, 2016

This memorandum provides the (b) (6) ((b) (6) review of the proposed modifications to the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) addressed in the (b) (6) ((b) (6) REMS Modification Review and Addendum to REMS Modification Review. A REMS for Mifeprex was approved on June 8, 2011, to ensure the benefits of the drug outweighed the risks of serious complications. The Mifeprex REMS consists of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Mifeprex was approved for the medical termination of an intrauterine pregnancy through 49 days of gestation on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (Subpart H). It was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the 2007 Food and Drug Administration Amendments Act. A formal REMS proposal was submitted by Danco and approved on June 8, 2011. The goals and elements of the approved Mifeprex REMS are briefly summarized in Table 1 below.

Table 1. Summary of Mifeprex REMS[1]

REMS Goals	To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
	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.
REMS Elements	Medication Guide
	ETASU A – Special certification of healthcare providers (HCPs) who prescribe Mifeprex: Completion of Prescriber's Agreement form and enrollment in the REMS program.
	ETASU C – Mifeprex is dispensed only in certain healthcare settings: It is only available to be dispensed in clinics, medical offices or hospitals, under the supervision of a specially certified prescriber. Mifeprex will not be distributed to or dispensed through retail pharmacies.
	ETASU D – Safe-use conditions: Patients must complete and sign the Patient Agreement form that is to be placed in the patient's medical record. A copy of the Patient Agreement form and Medication Guide must be provided to the patient.
Implementation System	Distributors of Mifeprex must be certified and agree to ship Mifeprex only to locations identified by certified prescribers. Distributors must agree to maintain secure and confidential records, as well as, follow all distribution guidelines concerning storage, shipments and controlled returns.

[1] Source: The (b) (6) REMS Modification Review (NDA 20867/S-020, dated March 29, 2016), Table 1.

On May 29, 2015, Danco submitted an efficacy supplement (S-020) that proposed modifications to the Mifeprex Prescribing Information and REMS. In the S-020 submission, Danco seeks the following major changes (among others):

- [redacted] dosing regimen of Mifeprex and misoprostol
- Extension of maximum gestational age from 49 days to 70 days
- Replacement of the term "licensed physician" with "[redacted] in the REMS Prescriber's Agreement form
- Removal of the phrase "Under Federal Law" from the REMS Prescriber's Agreement form
- Revisions to the Patient Agreement form reflecting changes to the Prescribing Information

The proposed changes in the efficacy supplement prompted revisions to the Mifeprex REMS materials and also updating of the REMS materials to current format. During review of this efficacy supplement, we also evaluated the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure the drug benefits outweigh the risks. The Agency considered the recent [redacted] REMS Assessment review completed October 13, 2015, safety data gathered since drug approval in 2000, and experience from current clinical practice to support additional modifications to the Mifeprex REMS.

After consultations between the [redacted] and [redacted] and considering the [redacted] REMS Modification Review and Addendum to the REMS Modification Review, [redacted] has determined that the approved REMS for Mifeprex should be modified as follows:

1. Revisions to the Prescriber's Agreement form in addition to those proposed by the Applicant
2. Removal of the Medication Guide as a REMS element
3. Removal of the Patient Agreement form as a Documentation of Safe Use Condition (ETASU D)
4. Updating of REMS goals to reflect the above changes

We concur with [redacted] recommendation that the Prescriber's Agreement form should include other modifications to reflect current REMS standards and materials and also to reflect changes to align with approval of the efficacy supplement S-020, such as the dose and dose regimen and upper limit of gestational age.

In addition, we agree with Danco's proposed removal of the phrase "Under Federal Law," because of the lack of precedent for requiring such text and clinical rationale for its inclusion. As approvals and REMS are governed by Federal law, the phrase "Under Federal law" is unnecessary. Regarding Danco's proposal to replace "licensed physician," we have determined that the replacement term should be "licensed healthcare providers who prescribe," to include other practitioners who prescribe; in addition, this phrase is consistent with language in the statute.

We concur with [redacted] recommendation that the Medication Guide is no longer necessary as an element of the REMS to ensure the benefits of Mifeprex outweigh its risks. The Medication Guide will continue to be part of the approved labeling that must be provided to a patient in accordance with 21 CFR part 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

In addition, we concur with [redacted] recommendation that the signed Patient Agreement form is no longer necessary and should be removed as a condition of safe use (ETASU D). Recent professional guidelines for women seeking surgical and medical abortion services emphasize comprehensive counseling, education about the risks of different treatments, and obtaining and documenting informed consent.[2,3] The National Abortion

[2] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

Federation (NAF) clinical practice guidelines include a standard stating that documentation must show that the patient affirms that she understands the procedure and its alternatives, the potential risks and benefits, and that her decision is voluntary.[4] Approximately (b)(4)% of the use of Mifeprex in the U.S. is through Planned Parenthood Federation of America (PPFA)- and NAF-affiliated members, where patient counseling and informed consent is standard of care. The practice of treating women with Mifeprex is well-established by these organizations and their associated providers who choose to provide this care to women. In addition, the Medication Guide, which must be provided to the patient under 21 CFR part 208, contains the same risk information contained in the Patient Agreement form.

The safety profile of Mifeprex is well-characterized and its risks well-understood after more than 15 years of marketing. Serious adverse events are rare and the safety profile of Mifeprex has not substantially changed.[5] The removal of the Medication Guide as a REMS element and of the Patient Agreement form is not expected to adversely impact the ability of the REMS to ensure that the drug benefits outweigh its risks. The benefit-risk balance of Mifeprex remains favorable in the presence of the following:

- Retention of ETASUs A and C in the Mifeprex REMS: The Prescriber's Agreement form required for prescriber certification under ETASU A will continue to require 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 by or under the supervision of a certified prescriber. This ensures that Mifeprex can only be dispensed by or under the direct supervision of a certified prescriber.

- Communication of risks through patient labeling: The Medication Guide, which will be retained as part of labeling, contains the same risk information covered under the Patient Agreement form. Under 21CFR 208.24, prescribers who dispense Mifeprex are required to provide the Medication Guide to patients. The Prescriber's Agreement form also reminds the prescriber to provide the Medication Guide to the patient.

- Information from published articles on established clinical practices: This information, including clinical guidelines and publications, indicates that comprehensive patient counseling and informed consent prior to medical or surgical abortion treatment is standard of care when using Mifeprex.

We have also determined that the information in the efficacy supplement supports changes to the goals of the Mifeprex REMS. We concur with (b) (6) recommendation that the REMS goals should be modified from:

A. To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
B. 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.

to:

The goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by:

a) Requiring healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program.

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[3] National Abortion Federation Membership information accessed on the internet at http://prochoice.org/health-care-professionals/naf-membership/ on March 11, 2016

[4] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf on March 11, 2016.

[5] (b) (6) Mifeprex Post-marketing Safety Review, dated August 20, 2015.

b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber.

The above REMS modifications and changes in goals were discussed with the (b) (6) and concurrence with these changes was obtained.

The modified Mifeprex REMS should consist of ETASU A, in which healthcare providers who prescribe Mifeprex will be certified, and ETASU C, in which Mifeprex will be dispensed only in certain health care settings (specially clinics, medical offices, and hospitals) by or under the supervision of a certified prescriber. The Mifeprex REMS will also include an implementation system, and a timetable for continued submission of assessments of the REMS.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked (b) (6) and (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 (b) (4), (b) (6) the Director, OSE, and (b) (6), to the Directors of (b) (6) and (b) (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, as described in the (b) (6) Addendum to REMS Modification Review.

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

Signing for (b) (6), (b) (6)

Exhibit O

MIFEPREX® (Mifepristone) Tablets, 200 mg

PRESCRIBER AGREEMENT FORM

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber 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 be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]

PRESCRIBER AGREEMENT FORM Mifepristone Tablets, 200 mg

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber 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 be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855—643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If mifepristone will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]

Exhibit P

MIFEPREX®(Mifepristone) Tablets, 200mg

PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
    - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
    - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
    - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
    - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
    - Track and verify receipt of each shipment of Mifeprex.
    - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
    - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
    - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
    - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
    - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
    - Train all relevant staff on the Mifepristone REMS Program requirements.
    - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

DANCO
Support • Progress • Options

P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343**.**

PHARMACY AGREEMENT FORM **Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
    - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
    - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
    - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
    - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
    - Track and verify receipt of each shipment of mifepristone.
    - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
    - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
    - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
    - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
    - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
    - Train all relevant staff on the Mifepristone REMS Program requirements.
    - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to **1-877-239-8036.**

Exhibit Q

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   - **a.** I will take mifepristone on Day 1.
   - **b.** I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am “feeling sick,” including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

Provider Signature: _____ **Provider Name** (print): _____ **Date**: _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

Exhibit R

MEDICATION GUIDE

Mifepristone (MIF-eh-pris-tone) tablets, 200 mg for oral use

Read this information carefully before taking Mifepristone tablets, 200 mg and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.

What is the most important information I should know about Mifepristone tablets, 200 mg?

What symptoms should I be concerned with? 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. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifepristone tablets, 200 mg and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.

Be sure to contact your healthcare provider promptly if you have any of the following:

- **Heavy Bleeding.** Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).
- **Abdominal Pain or "Feeling Sick."** If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
- **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.

If you cannot reach your healthcare provider, go to the nearest hospital emergency room.

What to do if you are still pregnant after Mifepristone tablets, 200 mg with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.

Talk with your healthcare provider. Before you take Mifepristone tablets, 200 mg, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifepristone tablets, 200 mg.

What is Mifepristone tablets, 200 mg?

Mifepristone tablets, 200 mg is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifepristone tablets, 200 mg is not approved for ending pregnancies that are further along. Mifepristone tablets, 200 mg blocks a hormone needed for your pregnancy to continue. When you use Mifepristone tablets, 200 mg on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifepristone tablets, 200 mg, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifepristone tablets, 200 mg and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifepristone tablets, 200 mg will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifepristone tablets, 200 mg?

Some patients should not take Mifepristone tablets, 200 mg. Do not take Mifepristone tablets, 200 mg if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifepristone tablets, 200 mg.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifepristone tablets, 200 mg.

What should I tell my healthcare provider before taking Mifepristone tablets, 200 mg?

Before you take Mifepristone tablets, 200 mg, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifepristone tablets, 200 mg can pass into your breast milk. The effect of the Mifepristone, tablets, 200 mg and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
  Mifepristone tablets, 200 mg and certain other medicines may affect each other if they are used together. This can cause side effects.

How should I take Mifepristone tablets, 200 mg?

- Mifepristone tablets, 200 mg will be given to you by a healthcare provider or pharmacy.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifepristone tablets, 200 mg and misoprostol:

Mifepristone tablets, 200 mg (1 tablet) orally + misoprostol (4 tablets) buccally

Day 1:

- Take 1 Mifepristone 200 mg tablet by mouth.

24 to 48 hours after taking Mifepristone tablets, 200 mg:

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifepristone tablets, 200 mg or later than 48 hours after Mifepristone tablets, 200 mg.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.

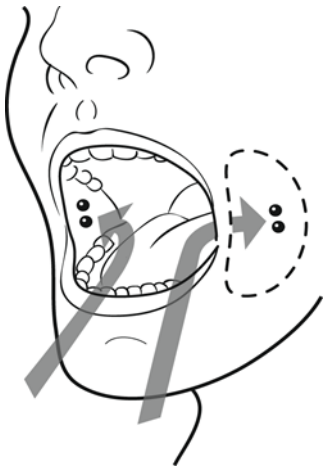

Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifepristone tablets, 200 mg to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifepristone tablets, 200 mg and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifepristone tablets, 200 mg and misoprostol?

Mifepristone tablets, 200 mg may cause serious side effects. See "What is the most important information I should know about Mifepristone tablets, 200 mg?"

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifepristone tablets, 200 mg. See "How should I take Mifepristone tablets, 200 mg?" for more information on your follow-up assessment. If you are not already bleeding after taking Mifepristone tablets, 200 mg, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifepristone tablets, 200 mg. Bleeding or spotting can be expected for an average of 9 to16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifepristone tablets, 200 mg treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects.These are not all the possible side effects of Mifepristone tablets, 200 mg.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifepristone tablets, 200 mg.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifepristone tablets, 200 mg. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifepristone tablets, 200 mg that is written for healthcare professionals.

For more information about Mifepristone tablets, 200 mg, go to www.MIFEINFO.com or call 1-855-MIFEINFO (1-855-643-3463).

Manufactured for:
GenBioPro, Inc.
P.O. Box 32011
Las Vegas, NV 89103
1-855-MIFEINFO (1-855-643-3463)
www.MIFEINFO.com

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Approval 01/2023

Exhibit S

Maureen G. Phipps, MD, MPH, FACOG
American College of Obstetricians and Gynecologists
409 12th Street SW
Washington, DC 20024

January 3, 2023

Re: Docket No. FDA-2022-P-2425

Dear Dr. Phipps:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on October 4, 2022, on behalf of the American College of Obstetricians and Gynecologists and 48 other organizations (Petition). In the Petition, you request that FDA:

(1) Ask Danco Laboratories, LLC, the holder of the approved new drug application (NDA) for Mifeprex (mifepristone) (NDA holder), to submit a supplemental new drug application (sNDA) that seeks to add miscarriage management as an indication to the drug's labeling, and to eliminate or modify mifepristone's risk evaluation and mitigation strategy (REMS) so that it is not unduly burdensome for that use

(2) Immediately exercise enforcement discretion with respect to the use and distribution of mifepristone for miscarriage management without complying with the REMS

We have carefully considered the Petition and other information available to us. For the reasons stated below, the Petition is denied.

I. BACKGROUND

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (NDA 020687). The application was approved under part 314, subpart H (21 CFR part 314, 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

[1] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.

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, an implementation system, and a timetable for submission of assessments of the REMS.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the NDA holder. 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 (through 70 days gestation), as well as the process for follow-up after administration of the drug.

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 milligrams (mg) (abbreviated new drug application 091178). As required by 21 CFR 314.94(a)(8), the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex.[3]

At the same time that FDA approved the generic version of Mifeprex in 2019, FDA approved a supplemental new drug application 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 January 2023, FDA approved another supplemental new drug application, approving modifications to the Mifepristone REMS Program to remove the requirement that mifepristone 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) and to add a pharmacy certification requirement.

II. DISCUSSION

A. Adding a New Indication to Mifeprex

In your Petition, you request that the Agency ask the NDA holder for Mifeprex to submit an sNDA that seeks to add miscarriage management as an indication to the drug's labeling (Petition at 1).[4]

---

[2] 73 FR 16313 (Mar. 27, 2008).

[3] 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.

[4] Your reference to FDA's request for submissions of NDAs to add an emergency contraception indication to certain combined oral contraceptives as precedent for FDA requesting that the NDA holder for Mifeprex add a management of miscarriage indication to its labeling is not on point (Petition at 1, footnote 1). The circumstances under which FDA made this request to manufacturers of oral contraceptives – which included unanimous backing by the

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations require that a person seeking to market a new drug, including a new indication for an approved drug, submit an application to FDA for review.[5] To support the addition of a new indication to a drug product's FDA-approved labeling, the holder of the NDA for the drug product would submit a supplemental application requesting a new indication.[6] FDA would approve a supplemental application only if the Agency finds that the drug product is safe and effective for the proposed indication.[7]

Only the holder of an approved application may submit a supplement to an application.[8] Therefore, if the person seeking a new indication for an approved drug product is not the application holder for the drug, that person would need to submit a separate, original application for approval of a new drug with the new indication.[9]

To support a finding of safety and effectiveness for a new indication, FDA would require, among other information, that an applicant provide adequate data and information to support the new indication. The applicant must establish effectiveness of the drug for the proposed indication and the application (whether an original application or a supplemental application) generally would contain data and information adequate to support a determination that the drug is safe and effective under the conditions of use specified in the labeling.

If the NDA holder for Mifeprex chooses to submit an sNDA to add an indication for miscarriage management to the Mifeprex labeling, the Agency will review such application consistent with the FD&C Act, FDA regulations, and our standard process for sNDAs. In addition, any person may submit an original new drug application requesting approval of mifepristone for miscarriage management.[10] As with all products, FDA is open to meeting with interested parties to discuss the potential submission of an application. In addition, it is our understanding that the NDA holder for Mifeprex is aware of your Petition, including the request to add miscarriage management as an indication to the drug's labeling.[11]

For these reasons, we deny your request that we ask the NDA holder for Mifeprex to submit an sNDA that seeks to add miscarriage management as an indication to the drug's labeling.

Advisory Committee for Reproductive Health Drugs in addition to specific findings by FDA based on literature and experience with approved combined oral contraceptive products – do not exist here.

[5] Section 505(a) of the FD&C Act (21 U.S.C. 355(a)) and 21 CFR part 314.

[6] §§ 314.71(b) and 314.50(d)(5). See also FDA final guidance, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (Dec. 2004), at 6. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] See section 505(d) of the FD&C Act.

[8] § 314.71(a).

[9] An application submitted under section 505(b)(1) of the FD&C Act, also called a "stand-alone NDA," requires that the application contain, among other information, "full reports of investigations" to show that the drug is safe and effective for its intended use.

[10] See section 505(b)(1) and (2) of the FD&C Act.

[11] See https://www.reuters.com/business/healthcare-pharmaceuticals/doctors-urge-us-fda-add-miscarriage-management-abortion-pill-label-2022-10-04/.

B. Mifepristone REMS Program

In your Petition, you ask that FDA eliminate or modify the Mifepristone REMS Program so that it is not unduly burdensome for a miscarriage management indication (Petition at 1). Because the management of miscarriage is not a currently approved indication for mifepristone, it would be premature for FDA to consider the impact that the addition of this indication would have, if any, on the Mifepristone REMS Program so that it is not unduly burdensome for that use.

For these reasons, we deny your request that we eliminate or modify the Mifepristone REMS Program so that it is not unduly burdensome for a miscarriage management indication.

In your Petition, you also request that FDA immediately exercise enforcement discretion with respect to the use and distribution of mifepristone for miscarriage management without complying with the REMS (Petition at 1).

The action you seek may not properly be the subject of a citizen petition under FDA's regulations. Under 21 CFR 10.30, a person may petition the Agency to issue, amend, or revoke a regulation or order or to take or refrain from taking any other form of administrative action. FDA regulations in 21 CFR 10.3 define "administrative action" as "every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner, except that it does not include the referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or an act in preparation of a referral." Similarly, under 21 CFR 10.30(k), citizen petitions may not be used with respect to "referral of a matter to a United States attorney for the initiation of court enforcement action and related correspondence." Agency decisions to take, or to refrain from taking, enforcement action are decisions related to the "referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings, or acts in preparation of such referrals" and therefore are not properly the subject of a citizen petition.

For these reasons, your request that FDA immediately exercise enforcement discretion with respect to the use and distribution of mifepristone for miscarriage management without complying with the Mifepristone REMS Program is denied.

III. CONCLUSION

For the reasons explained above, we deny your Petition.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2023.01.03 18:47:23 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

AO 440 (Rev. 06/12) Summons in a Civil Action

UNITED STATES DISTRICT COURT

for the

Eastern District of Washington

STATE OF WASHINGTON, et al.

Plaintiff(s)

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, et al.

Defendant(s)

Civil Action No.

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)* UNITED STATES FOOD AND DRUG ADMINISTRATION
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
OC-OCC-FDA-Litigation-Mailbox@fda.hhs.gov

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it) — or 60 days if you are the United States or a United States agency, or an officer or employee of the United States described in Fed. R. Civ. P. 12 (a)(2) or (3) — you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are: Andrew R.W. Hughes
Washington State Office of the Attorney General
800 Fifth Avenue, Suite 2000
Seattle, WA 98104-3188

If you fail to respond, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

CLERK OF COURT

Date

SEAN F. McAVOY, Clerk

Civil Action No.

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 4 (l))

This summons for *(name of individual and title, if any)* _____ was received by me on *(date)* _____ .

❒ I personally served the summons on the individual at *(place)* _____ on *(date)* _____ ; or

❒ I left the summons at the individual's residence or usual place of abode with *(name)* _____ , a person of suitable age and discretion who resides there, on *(date)* _____ , and mailed a copy to the individual's last known address; or

❒ I served the summons on *(name of individual)* _____ , who is designated by law to accept service of process on behalf of *(name of organization)* _____ on *(date)* _____ ; or

❒ I returned the summons unexecuted because _____ ; or

❒ Other *(specify):*

My fees are $ _____ for travel and $ _____ for services, for a total of $ 0.00 .

I declare under penalty of perjury that this information is true.

Date

Server's signature

Printed name and title

Server's address

Additional information regarding attempted service, etc:

Print Save As... Reset

AO 440 (Rev. 06/12) Summons in a Civil Action

UNITED STATES DISTRICT COURT

for the

Eastern District of Washington

STATE OF WASHINGTON, et al.

Plaintiff(s)

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, et al.

Defendant(s)

Civil Action No.

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)* ROBERT M. CALIFF
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
OC-OCC-FDA-Litigation-Mailbox@fda.hhs.gov

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it) — or 60 days if you are the United States or a United States agency, or an officer or employee of the United States described in Fed. R. Civ. P. 12 (a)(2) or (3) — you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are: Andrew R.W. Hughes
Washington State Office of the Attorney General
800 Fifth Avenue, Suite 2000
Seattle, WA 98104-3188

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AO 440 (Rev. 06/12) Summons in a Civil Action

UNITED STATES DISTRICT COURT

for the

Eastern District of Washington

STATE OF WASHINGTON, et al.

Plaintiff(s)

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, et al.

Defendant(s)

Civil Action No.

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)* UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
c/o General Counsel
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it) — or 60 days if you are the United States or a United States agency, or an officer or employee of the United States described in Fed. R. Civ. P. 12 (a)(2) or (3) — you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are: Andrew R.W. Hughes
Washington State Office of the Attorney General
800 Fifth Avenue, Suite 2000
Seattle, WA 98104-3188

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CLERK OF COURT

Date

SEAN F. McAVOY, Clerk

Civil Action No.

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AO 440 (Rev. 06/12) Summons in a Civil Action

UNITED STATES DISTRICT COURT

for the

Eastern District of Washington

STATE OF WASHINGTON, et al.

Plaintiff(s)

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, et al.

Defendant(s)

Civil Action No.

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)* XAVIER BECERRA, Secretary of Health and Human Services
c/o General Counsel
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it) — or 60 days if you are the United States or a United States agency, or an officer or employee of the United States described in Fed. R. Civ. P. 12 (a)(2) or (3) — you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are: Andrew R.W. Hughes
Washington State Office of the Attorney General
800 Fifth Avenue, Suite 2000
Seattle, WA 98104-3188

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CLERK OF COURT

Date

SEAN F. McAVOY, Clerk

Civil Action No.

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Server's address

Additional information regarding attempted service, etc:

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CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

STATE OF WASHINGTON, et al.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*

Attorney General of Washington, 800 Fifth Ave, Ste 2000
Seattle, WA 98104-3188, (206) 464-7744

DEFENDANTS

UNITED STATES FOOD AND DRUG ADMINISTRATION, et al.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☐ 3 Federal Question *(U.S. Government Not a Party)*
- ☒ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

Click here for: Nature of Suit Code Descriptions.

CONTRACT	TORTS		FORFEITURE/PENALTY	BANKRUPTCY	OTHER STATUTES
☐ 110 Insurance	**PERSONAL INJURY**	**PERSONAL INJURY**	☐ 625 Drug Related Seizure of Property 21 USC 881	☐ 422 Appeal 28 USC 158	☐ 375 False Claims Act
☐ 120 Marine	☐ 310 Airplane	☐ 365 Personal Injury - Product Liability	☐ 690 Other	☐ 423 Withdrawal 28 USC 157	☐ 376 Qui Tam (31 USC 3729(a))
☐ 130 Miller Act	☐ 315 Airplane Product Liability	☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability		**PROPERTY RIGHTS**	☐ 400 State Reapportionment
☐ 140 Negotiable Instrument	☐ 320 Assault, Libel & Slander	☐ 368 Asbestos Personal Injury Product Liability		☐ 820 Copyrights	☐ 410 Antitrust
☐ 150 Recovery of Overpayment & Enforcement of Judgment	☐ 330 Federal Employers' Liability	**PERSONAL PROPERTY**	**LABOR**	☐ 830 Patent	☐ 430 Banks and Banking
☐ 151 Medicare Act	☐ 340 Marine	☐ 370 Other Fraud	☐ 710 Fair Labor Standards Act	☐ 835 Patent - Abbreviated New Drug Application	☐ 450 Commerce
☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)	☐ 345 Marine Product Liability	☐ 371 Truth in Lending	☐ 720 Labor/Management Relations	☐ 840 Trademark	☐ 460 Deportation
☐ 153 Recovery of Overpayment of Veteran's Benefits	☐ 350 Motor Vehicle	☐ 380 Other Personal Property Damage	☐ 740 Railway Labor Act	☐ 880 Defend Trade Secrets Act of 2016	☐ 470 Racketeer Influenced and Corrupt Organizations
☐ 160 Stockholders' Suits	☐ 355 Motor Vehicle Product Liability	☐ 385 Property Damage Product Liability	☐ 751 Family and Medical Leave Act	**SOCIAL SECURITY**	☐ 480 Consumer Credit (15 USC 1681 or 1692)
☐ 190 Other Contract	☐ 360 Other Personal Injury		☐ 790 Other Labor Litigation	☐ 861 HIA (1395ff)	☐ 485 Telephone Consumer Protection Act
☐ 195 Contract Product Liability	☐ 362 Personal Injury - Medical Malpractice		☐ 791 Employee Retirement Income Security Act	☐ 862 Black Lung (923)	☐ 490 Cable/Sat TV
☐ 196 Franchise				☐ 863 DIWC/DIWW (405(g))	☐ 850 Securities/Commodities/ Exchange
				☐ 864 SSID Title XVI	☐ 890 Other Statutory Actions
				☐ 865 RSI (405(g))	☐ 891 Agricultural Acts
REAL PROPERTY	**CIVIL RIGHTS**	**PRISONER PETITIONS**			☐ 893 Environmental Matters
☐ 210 Land Condemnation	☐ 440 Other Civil Rights	**Habeas Corpus:**		**FEDERAL TAX SUITS**	☐ 895 Freedom of Information Act
☐ 220 Foreclosure	☐ 441 Voting	☐ 463 Alien Detainee		☐ 870 Taxes (U.S. Plaintiff or Defendant)	☐ 896 Arbitration
☐ 230 Rent Lease & Ejectment	☐ 442 Employment	☐ 510 Motions to Vacate Sentence		☐ 871 IRS—Third Party 26 USC 7609	☒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
☐ 240 Torts to Land	☐ 443 Housing/ Accommodations	☐ 530 General			☐ 950 Constitutionality of State Statutes
☐ 245 Tort Product Liability	☐ 445 Amer. w/Disabilities - Employment	☐ 535 Death Penalty	**IMMIGRATION**		
☐ 290 All Other Real Property	☐ 446 Amer. w/Disabilities - Other	**Other:**	☐ 462 Naturalization Application		
	☐ 448 Education	☐ 540 Mandamus & Other	☐ 465 Other Immigration Actions		
		☐ 550 Civil Rights			
		☐ 555 Prison Condition			
		☐ 560 Civil Detainee - Conditions of Confinement			

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District *(specify)* ☐ 6 Multidistrict Litigation - Transfer ☐ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
5 U.S.C. § 706; U.S. Const. 5th Amdt.

Brief description of cause:
APA and constitutional challenge to FDA regulations restricting access to mifepristone, a medicine used for medication abortions

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☐ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE
Feb 23, 2023

SIGNATURE OF ATTORNEY OF RECORD
Kristin Beneski

Digitally signed by Kristin Beneski
Date: 2023.02.23 13:17:17 -08'00'

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I.(a) **Plaintiffs-Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) **County of Residence.** For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) **Attorneys.** Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.Cv.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.
United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.
United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.
Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.
Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below**; NOTE: federal question actions take precedence over diversity cases.**)

III. **Residence (citizenship) of Principal Parties.** This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. **Nature of Suit.** Place an "X" in the appropriate box. If there are multiple nature of suit codes associated with the case, pick the nature of suit code that is most applicable. Click here for: Nature of Suit Code Descriptions.

V. **Origin.** Place an "X" in one of the seven boxes.
Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.
Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.
Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.
Multidistrict Litigation – Transfer. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407.
Multidistrict Litigation – Direct File. (8) Check this box when a multidistrict case is filed in the same district as the Master MDL docket.
PLEASE NOTE THAT THERE IS NOT AN ORIGIN CODE 7. Origin Code 7 was used for historical records and is no longer relevant due to changes in statue.

VI. **Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553 Brief Description: Unauthorized reception of cable service.

VII. **Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.
Demand. In this space enter the actual dollar amount being demanded or indicate other demand, such as a preliminary injunction.
Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. **Related Cases.** This section of the JS 44 is used to reference related pending cases, if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.