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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

v.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIVIL ACTION

Case No. 1-:17-cv-00493-JAO-RT

MOTION FOR LEAVE TO FILE AMENDED AND SUPPLEMENTAL COMPLAINT AND MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT

MOTION

Pursuant to the Court's February 28, 2023 Order (ECF 158), Plaintiffs hereby move the Court pursuant to Rule 15(a)(2) and 15(d) of the Federal Rules of Civil Procedure for leave to file an Amended and Supplemental Complaint to reflect events post-dating Plaintiffs' original complaint filed on October 3, 2017.

Plaintiffs principally seek leave to allege new and modified facts stemming from Defendant U.S. Food and Drug Administration's ("FDA") 2021–2023 review and 2023 reauthorization of the Mifepristone[1] REMS Program ("2023 REMS Reauthorization")—actions that occurred after, and resulted directly from, the filing of this litigation, and which continue to perpetuate many of the same harms and constitutional and Administrative Procedure Act ("APA") violations set out in Plaintiffs' original complaint. Plaintiffs' proposed Complaint also (1) removes one constitutional claim based on an intervening change in law under *Dobbs v. Jackson Women's Health Organization*, 142 S. Ct. 2228 (2022); (2) updates the parties by removing one plaintiff that was previously dismissed from the litigation and substituting defendants; (3) makes minor language adjustments to improve accuracy and clarity; and (4) updates the footnotes with more recent citations, including

[1] Plaintiffs use "mifepristone" to refer to both the brand-name drug, Mifeprex®, and its generic, mifepristone, which are subject to the same shared, single system REMS program.

citations to the administrative record wherever possible.[2]

Leave to amend and supplement should be "freely given" in the absence of undue and unexplained delay, bad faith, futility, or resulting prejudice to the other parties. Fed. R. Civ. P. 15(a)(2); *Howey v. United States*, 481 F.2d 1187, 1190 (9th Cir. 1973); *Pauline v. Espinda*, No. CIV. 13-00612 HG/RLP, 2014 WL 7366272, at *9 (D. Haw. Nov. 26, 2014) (same standard applies to motions to amend or to supplement). None of these factors apply here. For the reasons detailed in Plaintiffs' Memorandum of Points and Authorities, Plaintiffs respectfully request that the Court grant leave to file their Amended and Supplemental Complaint, attached as Exs. 1 (red-line) and 2 (clean), pursuant to Local Rule 10.4.

This motion is made following the conference of counsel pursuant to Local Rule 7.8, which took place on March 23, 2023. Plaintiffs previously provided notice of their intent to seek leave to file an Amended and Supplemental Complaint in a meet-and-confer on February 24, 2023, and in the Joint Status Report submitted on February 27, 2023, Joint Status Rep. ¶ 10 (ECF 157). Defendants have informed Plaintiffs through counsel that they will wait to review the proposed amended and

[2] For instance, Plaintiffs' Amended and Supplemental Complaint uses gender-neutral language to reflect the fact that "not all persons who may become pregnant identify as female," and that transgender and gender-non-binary people also need access to mifepristone. *Reprod. Health Servs. v. Strange*, 3 F.4th 1240, 1246 n.2 (11th Cir. 2021), *reh'g en banc granted, opinion vacated on other grounds sub nom. Reprod. Health Servs. ex rel. Ayers v. Strange*, 22 F.4th 1346 (11th Cir. 2022) (mem.). Similarly, FDA replaced language in the mifepristone REMS in 2019 with gender-neutral terms. *See* Pls.' Am. & Suppl. Compl. Ex. 2, ¶ 102.

supplemental complaint before deciding whether to take a position on this motion.

MEMORANDUM OF POINTS AND AUTHORITIES

I. BACKGROUND

Plaintiffs filed this litigation in 2017 challenging FDA's 2016 final agency action reauthorizing its restrictive REMS program for mifepristone, an FDA-approved prescription medication used in combination with the drug misoprostol to end an early pregnancy by initiating a process similar to a miscarriage. Since its original approval by FDA in 2000, 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." Amin. Record ("AR") 0539. Nevertheless, despite its well-documented safety and efficacy, FDA has long subjected mifepristone to a REMS program: a special set of restrictions layered on top of the normal protections that apply to virtually every other prescription drug.

Plaintiffs' original complaint challenged FDA's final agency action reauthorizing the mifepristone REMS in 2016. Congress permits FDA to impose a REMS *only* when necessary to ensure that a drug's benefits outweigh its risks based on specific, statutorily-defined factors, which Plaintiffs alleged were not met with respect to mifepristone. Compl. ¶¶ 47, 99–117 (ECF 1). Plaintiffs further alleged that FDA's imposition of the most burdensome type of REMS—Elements to Assure Safe Use ("ETASU")—was unlawful because FDA had not considered, and could

not show, that the ETASU were, *inter alia*, necessary because of the "inherent toxicity or potential harmfulness of [mifepristone]," "commensurate with the specific serious risk[s]" listed in the mifepristone labeling, and not "unduly burdensome on patient access." 21 U.S.C. § 355-1(f)(1)-(2); Compl. ¶¶ 49–51, 116–50. Plaintiffs brought three APA claims premised on these statutory violations as well as the arbitrariness of FDA's decision to impose a REMS with ETASU for mifepristone when the agency does not subject other comparably or less safe drugs to such restrictions. Compl. ¶¶ 230–40.

Plaintiffs also brought two constitutional claims: a substantive due process claim under the framework set out in *Roe v. Wade*, 410 U.S. 113 (1973), and its progeny, and an equal protection claim premised on FDA's singular and irrational treatment of patients seeking to obtain, and health care providers seeking to provide, mifepristone. Compl. ¶¶ 226–29. Plaintiffs sought a declaration that the mifepristone REMS is unlawful, and injunctive relief ordering FDA to permanently eliminate all of its REMS restrictions on mifepristone. *Id.* at 62–63.

Since the filing of this case, several significant developments have occurred relating to the mifepristone REMS. In 2020, a coalition of medical experts led by the American College of Obstetricians and Gynecologists ("ACOG") challenged one of the mifepristone ETASU in a separate matter, alleging that the ETASU requiring that mifepristone be dispensed only in a hospital, clinic, or medical office was

medically unnecessary and exposed patients to needless burdens and risks during the COVID-19 pandemic. As a result of that litigation, this ETASU was enjoined for six months. *ACOG v. FDA*, 472 F. Supp. 3d 183 (D. Md. 2020), *stayed*, 141 S. Ct. 578, 578 (2021) (mem.).

In April 2021, FDA announced that it would exercise enforcement discretion with respect to the mifepristone in-person dispensing ETASU for the duration of the COVID-19 public health emergency. *See* FDA, REMS Review Memorandum 6 (Jan. 3, 2023), attached hereto as Suppl. Ex. A (summarizing regulatory history). FDA acknowledged that, during the months when mifepristone was available through mail-order pharmacies under the preliminary injunction of the in-person dispensing ETASU, there was *no* increase in adverse safety events. *Id.* at 38.

In May 2021, Plaintiffs in the instant case moved for summary judgment. Shortly before its responsive brief was due, FDA notified Plaintiffs that it was undertaking a full review of the mifepristone REMS, and the parties jointly sought a stay—which this Court granted—on the condition that FDA would include in that "review any relevant data and evidence submitted by the Plaintiffs." Joint Mot. Stay 2 (ECF 148); Order Staying Case (ECF 149). Plaintiffs submitted data and evidence to FDA in two letters in August and September 2021 explaining why the mifepristone REMS is medically unjustified and burdens patients and health care systems. The letters, *inter alia*, cited opposition to the mifepristone REMS by

leading medical organizations, including the American Medical Association ("AMA") and ACOG; cited research and data demonstrating that mifepristone is extremely safe and remains so when available via normal prescription processes; and identified examples of other FDA-approved drugs that are less safe than, or comparably safe to, mifepristone but are not subject to a REMS. Letter from *Chelius* Plaintiffs to Janet Woodcock, MD (Sept. 29, 2021), attached hereto as Suppl. Ex. C; Letter from Soc'y of Family Planning to Christine Nguyen, MD (Aug. 13, 2021), attached hereto as Suppl. Ex. D.

In January 2023, FDA reauthorized the mifepristone REMS. While permanently eliminating the in-person dispensing requirement, FDA retained the other two ETASU—a requirement that the patient review and sign a counseling form that FDA's own scientific review team had recommended removing in 2016 because it is "duplicative" and "does not add to safe use conditions," AR 0437, 0674; and a requirement that providers be specially certified in order to prescribe mifepristone. In addition, FDA added a *new* ETASU requiring pharmacies to become certified before they can dispense mifepristone—a requirement that, notably, did not exist when pharmacies dispensed mifepristone throughout the pandemic with no increase in adverse events. *See* Risk Evaluation & Mitigation Strategy (REMS) Single Shared System for Mifepristone (2023), attached hereto as Suppl. Ex. E.

Plaintiffs now move to amend and supplement their complaint to reflect

FDA's actions subsequent to the filing of the original complaint, including the 2023 REMS Reauthorization—a new final agency action that, like the 2016 action Plaintiffs challenged in their original complaint, continues to irrationally and unconstitutionally restrict and burden patients' access to an extremely safe and effective medication used for early abortion as well as miscarriage care. Plaintiffs also move to amend the complaint to drop a claim based on the intervening change in law under *Dobbs*; drop a dismissed plaintiff; substitute defendants; and make other minor updates and adjustments.

As evidenced in the red-lined complaint attached as Exhibit 1, Plaintiffs propose three kinds of edits: (1) minor line-edits to improve accuracy and precision, including by updating the footnotes; (2) one entirely new section, and several additional paragraphs elsewhere in the pleading, summarizing developments post-dating the original 2017 filing; and (3) replacements of two sections in the original complaint—the preliminary statement and the section on harm, Am. & Suppl. Compl., Ex. B ¶¶ 1–20, 169–212—where attempting to shoehorn the current impact of the 2023 REMS into the exact narrative structure of the original complaint would have needlessly reduced clarity and readability for the Court.

II. ARGUMENT

Amendment and supplementation of pleadings serve related and complementary purposes. Amendments "relate to matters that occurred prior to the

filing of the original pleading and entirely replace the earlier pleading." 6A Charles A. Wright, Arthur R. Miller, & Mary K. Kane, Fed. Prac. & Proc. Civ. § 1504 (3d ed.). Supplementation "deal[s] with events subsequent to the pleading to be altered and represent additions to or continuations of the earlier pleadings." *Id.*; *see also* Fed. R. Civ. P. 15(d) (leave to supplement a pleading based on "any transaction, occurrence, or event that happened after the date of the pleading" may be granted "on just terms"). Supplementation to capture relevant developments post-dating an original complaint serves the "basic aim of the rules to make pleadings a means to achieve an orderly and fair administration of justice," *Griffin v. Cnty. Sch. Bd. of Prince Edward Cnty.*, 377 U.S. 218, 226 (1964), and "promote[s] as complete an adjudication of the dispute between the parties as possible by allowing the addition of claims which arise after the initial pleadings are filed," *William Inglis & Sons Baking Co. v. ITT Cont'l Baking Co.*, 688 F.2d 1014, 1057 (9th Cir. 1981).

Courts apply the same liberal standard in evaluating motions to amend under Rule 15(a)(2) and motions to supplement under Rule 15(d). *Pauline*, 2014 WL 7366272, at *9; *see also* 6A Wright, Miller & Kane § 1504 ("[T]he distinction between amended and supplemental pleadings is sometimes ignored completely"). Leave to amend and supplement should be applied with "extreme liberality." *Sonoma Cnty. Ass'n of Retired Emps. v. Sonoma County*, 708 F.3d 1109, 1117 (9th Cir. 2013); *accord DCD Programs, Ltd. v. Leighton*, 833 F.2d 183, 186 (9th Cir.

1987) (citation omitted); *see also* Fed. R. Civ. P. 15(a)(2) (courts should "freely give leave [to amend] when justice so requires"). The U.S. Supreme Court has held that "the rules require" leave be given "[i]n the absence of any apparent or declared reason" for denial. *Foman v. Davis*, 371 U.S. 178, 182 (1962).

In determining whether to grant leave to amend, courts must look for "strong evidence" of the following factors: (1) undue delay; (2) bad faith or dilatory motive on the part of the movant; (3) repeated failure to cure deficiencies by amendments previously allowed; (4) futility of amendment; or (5) undue prejudice to the opposing party by virtue of allowance of the amendment. *Sonoma Cnty. Ass'n of Retired Emps.*, 708 F.3d at 1117 (quoting *Foman*, 371 U.S. at 182); *accord Lockheed Martin Corp. v. Network Sols., Inc.*, 194 F.3d 980, 986 (9th Cir. 1999); *Howey*, 481 F.2d at 1190; *Pauline*, 2014 WL 7366272, at *9. All inferences must be drawn in favor of the moving party, *Griggs v. Pace Am. Grp., Inc.*, 170 F.3d 877, 880 (9th Cir. 1999), and the party opposing the motion bears the burden of demonstrating a reason for denial, *see DCD Programs, Ltd.*, 833 F.2d at 187. None of the factors weighing against granting leave to amend and supplement are present here.

A. Plaintiffs Seek to Supplement Their Complaint Based on Events Post-Dating Their Original Filing, Consistent with FRCP 15(d).

This case presents a paradigmatic example of when supplementation is appropriate under FRCP 15(d): Plaintiffs seek to update their complaint to capture events post-dating their 2017 filing that are highly relevant to the allegations, claims,

and requests for relief in their original filing—including actions FDA took as a direct result of this litigation.[3] It is well-established that leave to supplement is permissible under such circumstances. *E.g.*, *United States v. Springer*, 491 F.2d 239, 241–42 (9th Cir. 1974) (holding that Rule 15(d) authorized supplemental pleading where the Board of Land Appeals issued a final agency action impacting the central issue of the case and did so after "the date of the [initial] pleading sought to be supplemented"); *Keith v. Volpe*, 858 F.2d 467, 474, 476 (9th Cir. 1988) (allowing supplemental pleading under Rule 15(d) based on new actions of Defendant and where relationship existed "between the newly alleged matters and the subject of the original action").

B. Plaintiffs' Motion is Timely and in Good Faith.

Plaintiffs file this Motion less than three months after FDA's 2023 REMS Reauthorization and consistent with this Court's Order directing such a filing by March 30, 2023 (ECF 158).

At every step of the way, Plaintiffs have acted in good faith. On January 4, one day after FDA released its updated REMS, Plaintiffs' counsel emailed counsel

[3] *Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation*, U.S. Food & Drug Admin. (last updated Jan. 4, 2023), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation (stating, under question 29 in the "Litigation and Other Legal Issues" section, that "[t]he agency's comprehensive review of the Mifepristone REMS Program, which led to the agency's December 16, 2021, decision that a modification is required, was related to the litigation in *Chelius v. Becerra*").

for Defendants to acknowledge the changed circumstances and note that FDA's updated REMS Review memoranda were not yet publicly available. Explaining that Plaintiffs "cannot make decisions about next steps with the litigation without seeing that analysis," they asked for defense counsel's assistance gaining access to those materials. On January 17, Defendants responded with instructions to locate those memoranda on FDA's website. Since then, Plaintiffs have been working diligently to review the materials FDA has made publicly available (nearly 200 pages) regarding its 2023 REMS Reauthorization; to investigate the nature and scope of the ongoing harm posed by the updated REMS, including the new Pharmacy Certification ETASU that did not exist until 2023; and to identify specific members of the Plaintiff organizations who continue to face barriers as a result of the REMS and are willing to be publicly identified in a case relating to abortion. *See Jackson v. Bank of Hawaii,* 902 F.2d 1385, 1388 (9th Cir. 1990) (in assessing timeliness, considering whether the plaintiffs "knew or should have known the facts and theories raised by the amendment in the original pleading"). Under these circumstances, leave to amend and supplement is plainly proper, notwithstanding that this "litigation has been ongoing for several years." *Sonoma Cnty. Ass'n of Retired Emps.,* 708 F.3d at 1117–18. "The mere fact that an amendment is offered late in the case . . . is not enough to bar it," particularly where, as here, the "theory and the operative facts of the claim remain the same." *Id.* (internal quotations omitted).

C. Plaintiffs Have Not Failed to Cure Deficiencies by Previous Amendments.

This factor has no application here. Plaintiffs do not seek to amend and supplement their Complaint in order to cure deficiencies, but rather to reflect changed circumstances post-dating their 2017 filing. Any other minor adjustments Plaintiffs propose making are tertiary measures that Plaintiffs would not pursue if not for the need to otherwise update the pleading and are designed only to enhance readability and precision.

D. Amendment Would Not Be Futile.

A proposed amendment is futile only "[i]f no amendment would allow the complaint to withstand dismissal as a matter of law." *Kroessler v. CVS Health Corp.*, 977 F.3d 803, 815 (9th Cir. 2020). Here, Plaintiffs' Amended and Supplemental Complaint—like their original Complaint—contains more than sufficient factual matter, accepted as true, to "state a claim to relief that is plausible on its face." *Id.* at 807 (quoting *Weber v. Dep't of Veteran Affairs*, 521 F.3d 1061, 1065 (9th Cir. 2008)). Indeed, Plaintiffs have alleged in great detail—with extensive citation to public-facing materials and to the administrative record—why FDA's continued imposition of the mifepristone REMS and its ETASU exceeds the agency's statutory authority and arbitrarily singles out mifepristone patients and prescribers in violation of the U.S. Constitution and the APA. Amendment would not be futile.

E. Defendants Will Not Be Unduly Prejudiced.

To justify denial of leave to amend, any prejudice to Defendants must be substantial. *See Morongo Band of Mission Indians v. Rose*, 893 F.2d 1074, 1079 (9th Cir. 1990) (finding that proposed amended claims under a multitude of federal statutes presented a "radical shift in direction" with "tenuous nature" to the original complaint such that amendment would unduly prejudice defendants). The additional facts that Plaintiffs allege do not transform the nature of the case or require Defendants to pursue a new defense strategy. Rather, Plaintiffs' supplemental complaint is essential to inform the Court of actions that FDA has taken since the filing of this action and the ways in which those actions affect (and in some instances narrow) the issues and claims before the Court. Defendants "should be fully prepared to litigate the substantive issues of the claim." *See Sonoma Cnty. Ass'n of Retired Emps.,* 708 F.3d at 1118; *see also LaSalvia v. United Dairymen of Arizona*, 804 F.2d 1113, 1119 (9th Cir. 1986) (amendment would not unduly prejudice Defendant because "most of the information on the added claim would be available in [Defendant's] own files" and thus any additional discovery was "minimal."). Defendants will not be prejudiced by amendment or supplementation.

III. CONCLUSION

This Court should grant Plaintiffs' motion for leave to amend and supplement their complaint.

Respectfully submitted,

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EXHIBIT 1

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., ~~*on behalf of himself and his patients; SOCIETY OF FAMLY PLANNING, on behalf of its members and their patients; CALIFORNIA ACADEMY OF FAMILY PHYSICIANS, on behalf of its members and their patients; and PHARMACISTS PLANNING SERVICES INC., on behalf of its members and their patients,*~~*et al.*,

Plaintiffs,

v.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,
~~DON J. WRIGHT, M.D., M.P.H., in his official capacity as ACTING SECRETARY, UNITED STATES~~

CIVIL ACTION

Case No. ~~1:17-cv-~~00493-JAO-RT~~-----~~

AMENDED AND SUPPLEMENTAL COMPLAINT

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~~DEPARTMENT OF HEALTH AND HUMAN SERVICES, and his employees, agents and successors in office; UNITED STATES FOOD AND DRUG ADMINISTRATION; and SCOTT GOTTLIEB, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, and his employees, agents and successors in office,~~

Defendants.

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Plaintiffs, by and through their undersigned attorneys, bring this complaint against the above-named Defendants, their employees, agents, and successors in office, and in support thereof allege the following:

PRELIMINARY STATEMENT

1. Mifepristone is a prescription medication that U.S. patients have used for decades to end an early pregnancy by initiating a process very similar to a miscarriage.[1] As the U.S. Food and Drug Administration ("FDA" or "the Agency") observed 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]

2. Indeed, safety data from mifepristone's 5.6 million uses in the United States confirm that it is far safer than many other common medications, including Tylenol and Viagra.[3]

3. Moreover, FDA has never concluded that any very rare serious complications were actually caused by mifepristone. To the contrary, mifepristone's FDA-

[1] Plaintiffs use "mifepristone" to refer to both the brand-name drug, Mifeprex®, and its generic, mifepristone, which are subject to identical regulations.

[2] Admin. Record ("AR") 0539.

[3] U.S. Food & Drug Admin., Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2022, *available at* https://www.fda.gov/media/164331/download [hereinafter "Mifepristone U.S. Post-Marketing Adverse Events"].

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approved labeling notes that the serious risks identified in mifepristone's labeling are the same risks arising any time the pregnant uterus is emptied, whether through childbirth, miscarriage, or abortion.[4] And FDA has explained that in nearly all of the (very few) cases of fatal infections associated with mifepristone, the "critical risk factor . . . is pregnancy itself."[5]

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4. Nevertheless, FDA subjects mifepristone to a Risk Evaluation and Mitigation Strategy ("REMS"), which is a special set of restrictions above and beyond the normal layers of protections that apply to virtually every other prescription drug.

5. Congress permits FDA to impose a REMS *only* when "necessary to ensure that the benefits of a drug outweigh [its] risks," considering certain statutorily mandated factors. 21 U.S.C. §355-1(a)(1). Congress established further safeguards around the imposition of the most burdensome kinds of REMS—Elements To Assure Safe Use ("ETASU")—which FDA may impose only when necessary because of the "inherent toxicity or potential harmfulness" of a drug. *Id.* § 355-1(f)(1). Specifically, FDA may impose ETASU on a drug that "has been shown to be effective" only if it is "associated with a serious adverse drug experience" such that it "can be approved only if, or [approval] would be withdrawn unless, such [ETASU] are required." *Id.* § 355-1(f)(1)(A). Even then, ETASU must be

[4] AR 0398.

[5] AR 880–81 & n.69.

"*commensurate* with the specific serious risk[s]" listed in the drug's labeling, *id.* § 355-1(f)(2)(A); "required as part of [a] strategy to *mitigate*" such risks, *id.* § 355-1(f)(1)(A); and not "*unduly burdensome* on patient access to the drug, considering in particular . . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)," *id.* § 355-1(f)(2)(C) (emphases added).

6. FDA imposes a REMS on fewer than 3% of the more than 20,000 drug products it regulates, and 75% of drugs subject to a REMS are opioids[6]—which "are claiming lives at [such] a staggering rate" that they "are reducing life expectancy in the United States."[7]

7. In 2017, Plaintiffs filed this litigation challenging FDA's 2016 final agency action reauthorizing a REMS, including three ETASU, for mifepristone.

8. In 2020, a coalition of medical experts led by the American College of Obstetricians and Gynecologists ("ACOG") challenged one of the mifepristone ETASU in a separate matter: *ACOG v. FDA*, 472 F. Supp. 3d 183 (D. Md. 2020). The plaintiffs in *ACOG* argued that FDA's longstanding requirement that mifepristone be dispensed only in a hospital, clinic, or medical office was medically unnecessary and exposed patients to needless burdens and viral risks during the

[6] Joint Stip. of Facts ¶¶ 58–59; (ECF 85).

[7] *Opioid Medications*, U.S. Food & Drug Admin., https://www.fda.gov/drugs/information-drug-class/opioid-medications (last updated Mar. 29, 2021).

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COVID-19 pandemic. *Id.* The U.S. District Court for the District of Maryland preliminarily enjoined this ETASU over defendants' 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. That injunction remained in place for six months. *FDA v. ACOG*, 141 S. Ct. 578, 578 (2021) (mem.) (granting stay).

9. In April 2021, FDA announced that it would exercise enforcement discretion with respect to the mifepristone in-person dispensing ETASU for the duration of the COVID-19 Public Health Emergency.[8] The Agency conceded that, during the six-month period when the in-person dispensing requirement was enjoined and mifepristone was available through mail-order pharmacies, there was *no* increase in adverse safety events.[9]

10. The next month, in May 2021, Plaintiffs in the instant case moved for summary judgment. Shortly before FDA's brief was due, the Agency notified

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[8] U.S. Food & Drug Admin., REMS Review Memorandum 6 (Jan. 3, 2023) [hereinafter "2023 REMS Review"], attached hereto as Suppl. Ex. A (summarizing regulatory history).

[9] U.S. Food & Drug Admin., REMS Review Memorandum 38 (Dec. 16, 2021) [hereinafter "2021 REMS Review"], attached hereto as Suppl. Ex. B ("We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.").

Plaintiffs that it was undertaking a new review of the mifepristone REMS. On the condition that FDA would "review any relevant data and evidence submitted by the Plaintiffs," Joint Mot. Stay 2 (ECF 148), the parties jointly moved for a stay.

11. In August and September 2021, Plaintiffs submitted to FDA two letters explaining why the mifepristone REMS is medically unjustified and burdens patients and the health care system. Plaintiffs cited statements opposing the mifepristone REMS by other leading medical associations, including the American Medical Association ("AMA"), ACOG, and the American Academy of Family Physicians ("AAFP"),[10] And, among other research, Plaintiffs cited data showing that after Canada eliminated its restrictions on mifepristone in 2017 to allow for normal prescribing, medication abortion remained extremely safe, with a major complication rate of only 0.33%.[11]

12. In addition, Plaintiffs gave examples of other medications that pose risks greater than or comparable to that of mifepristone but are *not* subject to a REMS. For instance, Plaintiffs noted that Jeuveau® is not subject to a REMS, even though it is used for a purely cosmetic purpose—temporarily reducing the appearance of

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[10] *See generally* Letter from *Chelius* Plaintiffs to Janet Woodcock, MD (Sept. 29, 2021) [hereinafter "*Chelius* Plaintiffs' Letter"], attached hereto as Suppl. Ex. C; Letter from Soc'y of Family Planning to Christine Nguyen, MD (Aug. 13, 2021) [hereinafter "SFP Letter"], attached hereto as Suppl. Ex. D.

[11] *Chelius* Plaintiffs' Letter, *supra* note 10, at 2.

lines between one's eyebrows—and carries an FDA black-box warning for "[s]wallowing and breathing difficulties" that "can be life threatening," with "reports of death."[12]

13. In January 2023, FDA reauthorized the mifepristone REMS.[13] While permanently eliminating in-person dispensing, FDA retained the other two ETASU—including one that the Agency's own scientific review team had recommended removing in 2016 because it is "duplicative" and "does not add to safe use conditions."[14] Moreover, FDA added a *new* ETASU requiring pharmacies to become "certified" before they can dispense mifepristone—notwithstanding that pharmacies had dispensed mifepristone throughout the pandemic with no certification requirement and no increase in adverse events.

14. FDA's REMS Review memoranda reflect that, in reauthorizing the REMS in 2023, the Agency nowhere considered many of the statutory factors Congress requires to inform a decision whether to impose a REMS and ETASU, such as the "background incidence" of adverse events in the population likely to use the drug and whether the drug is a "new molecular entity" posing potentially unknown risks.

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[12] *Id.* at 3.

[13] Risk Evaluation & Mitigation Strategy (REMS) Single Shared System for Mifepristone (2023), attached hereto as Suppl. Ex. E.

[14] AR 0437, 0674.

21 U.S.C. § 355-1 (a)(1). Accordingly, the Agency never grappled with facts critical to the mifepristone REMS analysis—including FDA's admissions that continuing a pregnancy is many times more dangerous than ending a pregnancy with mifepristone and misoprostol;[15] that the risks associated with mifepristone are inherent to pregnancy and have never been shown to be caused by mifepristone rather than by pregnancy itself;[16] and that mifepristone is a very common and well-studied medication with an extremely strong and stable risk profile.[17]

15. FDA also nowhere explained how its ETASU could possibly be "commensurate" with the risks listed in the mifepristone labeling when FDA does not impose similar restrictions on other, riskier drugs. 21 U.S.C. § 355-1(f)(2)(A).

16. And FDA expressly declined to consider, *inter alia*, the positions of leading medical associations that the mifepristone REMS is not supported by science and harms patients and the health care system; and evidence showing that the mifepristone ETASU are "unduly burdensome on patient access to the drug," particularly for "patients in rural or medically underserved areas" who struggle to

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[15] AR 0859 & n.6 (FDA relying on study finding that "the risk of childbirth related death was therefore approximately 14 times higher than the rate associated with legal abortion").

[16] AR 383–84, 0387, 0398.

[17] *See, e.g.*, 2021 REMS Review, *supra* note 9, at 22, 31; AR 0535 (after 15 years of mandatory adverse event reporting under the REMS, FDA "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");; AR 0574 (major adverse events associated with mifepristone are "exceedingly rare").

obtain abortion care. *Id.* § 355-1(f)(2)(C).

17. At bottom, FDA's latest REMS analyses—just like the 2016 REMS decision Plaintiffs originally challenged—assumes without supporting data that the restrictions the Agency put in place long ago, when mifepristone was still a novel drug in the United States, remain necessary after millions of uses and mountains of evidence confirming mifepristone's safety and efficacy.

18. The elimination of in-person dispensing—a decision FDA made only *after* a federal court injunction confirmed that the Agency's speculative safety concerns were unfounded—removed one key barrier that had prevented clinicians, including Plaintiff Dr. Graham Chelius, from prescribing mifepristone at all, as well as forcing countless patients to travel unnecessarily when they could otherwise safely obtain their prescription through telemedicine and by mail.

19. Nevertheless, the 2023 REMS continues to significantly impede patients' access to mifepristone—including by (1) creating an administrative morass for clinicians seeking to integrate mifepristone into their health care systems, delaying or altogether derailing their efforts to provide this care; (2) posing logistical and technological challenges that amount to a *de facto* in-person pill pick-up requirement for some patients, most often those with lower incomes; (3) deterring qualified clinicians from prescribing mifepristone because they fear anti-abortion violence and harassment if their registration as a mifepristone prescriber were ever exposed;

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(4) deterring pharmacies from dispensing mifepristone because of the burdens of certification; (5) impeding research and training on mifepristone at academic institutions because of stigma arising from a REMS classification; and (6) undermining the informed consent process and provider-patient relationship by mandating counseling that is at best duplicative—and often inaccurate, confusing, and distressing.

~~1.~~ In the wake of the U.S. Supreme Court's decision in *Dobbs v. Jackson Women's Health Org.*, 142 S. Ct. 2228 (2022), abortion access is decimated in much of the country and the United States faces a growing maternal mortality crisis, particularly for people of color. Against that backdrop, there is an ever more urgent need to eliminate FDA's medically unjustified restrictions on mifepristone, which needlessly reduce health care capacity and burden patients in those states where abortion access remains lawful, but is under tremendous strain.

~~2.~~20.

~~1. Since 2000, mifepristone has been approved by the United States Food and Drug Administration ("the FDA" or "the Agency") under the brand name Mifeprex® for use, in a regimen with the drug misoprostol, as a medical option for terminating an early pregnancy. Mifeprex remains the only drug approved in the United States for this purpose and is commonly referred to as the "abortion pill." Over the past 17 years, 3 million women in the United States have used Mifeprex~~

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to end an early pregnancy. According to the FDA, this medication "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."[18] Within a few days of taking Mifeprex and then misoprostol, the patient will experience a miscarriage. These prescription medications enable a woman to end a pregnancy up to 10 weeks in the privacy and comfort of her home.

2. This case is not about whether Mifeprex should continue to be available only by prescription. Rather, this case is about where a woman must be standing when she receives the pill her health care provider has prescribed for her. The unique and harmful restrictions the FDA imposes on where and how a patient may receive Mifeprex deny women meaningful access to this safe and effective treatment with no medical justification.

3. Mifeprex is safe. As the FDA concluded in March 2016, serious adverse events following Mifeprex use are "exceedingly rare," and "the numbers of these adverse events appear to be stable or decreased over time."[19]

4. Indeed, the risks associated with Mifeprex are lower than those of many other common medications, such as Viagra® or anticoagulants (blood thinners).

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[18] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Mifeprex Medical Review(s) 12 (Mar. 29, 2016) [hereinafter "2016 Medical Review"], attached hereto as Ex. A.

[19] *Id.*, Ex. A, at 47.

Mifeprex use is also far safer than continuing a pregnancy: the risk of associated fatality is *fourteen times greater* for a woman who carries a pregnancy to term than for a woman who uses Mifeprex.

5. Moreover, because Mifeprex is prescribed and administered as a single pill, there is no risk of a patient developing a dependency (as there is for many widely used prescription drugs).

6. Yet despite the fact that serious adverse events associated with Mifeprex are "exceedingly rare," and despite what the FDA recognizes as the "meaningful therapeutic benefit" that Mifeprex provides to patients seeking to end an early pregnancy using pills rather than a surgical procedure,[20] the FDA subjects Mifeprex to a Risk Evaluation and Mitigation Strategy ("REMS") that burdens health care providers and limits patient access to this medication with no medical benefit.

7. A REMS is a set of requirements beyond the approved prescribing information that the FDA may impose under the federal Food, Drug, and Cosmetic Act ("FDCA") The most burdensome type of REMS are "Elements to Assure Safe Use" ("ETASU"), which the FDA may impose only when necessary because of the

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[20] Letter from Janet Woodcock, M.D., Director, Ctr. for Drug Evaluation & Research, to Donna Harrison, M.D., *et al.*, Denying Citizen Petition Asking the FDA to Revoke Approval of Mifeprex 4 (Mar. 29, 2016) [hereinafter "Letter Denying Petition to Revoke Mifeprex Approval"], attached hereto as Ex. B.

"inherent toxicity or potential harmfulness" of a drug. *Id.* § 355-1(f)(1). Specifically, the FDA may impose ETASU on a drug that "has been shown to be effective" only if it is "associated with a serious adverse drug experience" such that it "can be approved only if, or [approval] would be withdrawn unless, such elements are required." *Id.* § 355-1(f)(1)(A). And, even then, the ETASU must be "*commensurate* with the specific serious risk[s]" listed in the drug label, *id.* § 355-1(f)(2)(A); "required as part of [a] strategy to *mitigate*" such risks, *id.* § 355-1(f)(1)(A); and not "*unduly burdensome* on patient access to the drug, considering in particular . . . . patients in rural or medically underserved areas," *id.* § 355-1(f)(2)(C) (emphases added).

8. In light of these stringent statutory limitations, of the nearly 1800 prescription drugs and therapeutic biologic active ingredients currently approved by the FDA and marketed in the U.S.,[21] only 73 are subject to a REMS—and just 43 are subject to a REMS *with* ETASU.[22]

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[21] Elizabeth G. Raymond *et al.*, *Sixteen Years of Overregulation: Time to Unburden Mifeprex*, 376 New Eng. J. Med. 790, 790 (2017).

[22] U.S. Food & Drug Admin., Approved Risk Evaluation and Mitigation Strategies (REMS), https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsData.page (last visited Oct. 1, 2017) [hereinafter "FDA REMS Count"].

9. Nevertheless, in violation of the FDCA, Mifeprex is subject to a REMS with ETASU that significantly restricts how it can be distributed without any corresponding medical benefit.[23]

10. Specifically, the Mifeprex REMS provides that a patient cannot obtain the medication by prescription at a retail pharmacy, as is the normal course. Rather, she must be handed the medication at a clinic, medical office, or hospital under the supervision of a health care provider who has registered with the drug manufacturer, attested to their ability to safely prescribe Mifeprex, and then arranged to order and stock Mifeprex in their health care facility. In addition, the patient must sign a "Patient Agreement" form confirming that she has received counseling on the risks associated with Mifeprex.

11. Thus, a woman who turns to her trusted local health care provider with an unwanted pregnancy and requests a medication abortion cannot obtain that care unless the clinician has already registered with the drug manufacturer and arranged to stock the drug. This is so even though that same provider can simply write her a prescription for misoprostol, the second drug in the FDA's approved regimen for medication abortion, or virtually any other prescription drug that the clinician deems medically appropriate.

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[23] Mifeprex Risk Evaluation and Mitigation Strategy (REMS) (2016), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf (last visited Oct. 1, 2017) [hereinafter "Current Mifeprex REMS"].

~~12. For many health care providers across the country, registering with the drug manufacturer and stocking Mifeprex at their office is difficult or impossible. Some cannot obtain approval from their hospital's bureaucracy because of opposition to abortion. Some fear the internal conflict that would arise if colleagues opposed to abortion were asked to be involved in procuring, stocking, or dispensing the abortion pill. Some are deterred by the logistics of being "certified" by a drug manufacturer, entering into a contract with the drug distribution company, and ordering the medication—a process unfamiliar to many clinicians because it is required for such a small number of drugs, and which can be particularly complicated and time-consuming for clinicians at large health care institutions. Others are uncomfortable having their names included on a master list of medication abortion providers in the country, fearful of anti-abortion violence or harassment if the list were ever exposed.~~

~~13. The Mifeprex REMS does not improve patient health or safety. Once a woman has been prescribed Mifeprex, there is no medical benefit to requiring that the pill be handed to her at a medical office, clinic, or hospital rather than handed to her at her local pharmacy or via a mail-order pharmacy. Indeed, the Mifeprex REMS does not require that a patient *take* the medication at the health care facility; as long as the drug is dispensed at an authorized medical setting, she may take the~~

drug with her for later use at home, which some women find desirable if it would be unsafe or inconvenient to experience a miscarriage in the next 24 to 72 hours.

14. Moreover, having found that "[h]ome administration . . . is efficacious, practical, and safe," the FDA allows a woman to receive the misoprostol (the second drug in the approved regimen, which causes uterine contractions and expulsion of the pregnancy) at a retail pharmacy and take it at home in the timeframe and manner her health care provider instructs.[24] And the FDA authorizes patients to self-administer at home another, less safe, mifepristone product, Korlym®, as treatment for Cushing's syndrome—even though, as the FDA noted, 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."[25]

15. As for the Mifeprex Patient Agreement requirement, the FDA's own team of expert reviewers uniformly recommended in 2016 that this REMS element be eliminated because it is duplicative of informed consent laws and standards, "does not add to safe use conditions . . . and is a burden for patients."[26] However, they

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[24] 2016 Medical Review, *supra* note 1, Ex. A, at 22.

[25] *Id.*, Ex. A, at 10.

[26] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Mifeprex Summary Review 25 (Mar. 29, 2016) [hereinafter "2016 Summary Review"], attached hereto as Ex. C.

were overruled by then-FDA Commissioner Robert Califf, M.D., and this ETASU was reauthorized in March 2016.[27]

16. Similarly, the requirement that clinicians sign a form stating that they are competent to prescribe Mifeprex provides no additional safety benefit beyond that conferred by the numerous laws and standards already in place to ensure that health care providers practice only within their competency. It is also out of step with how the FDA regulates other, less safe medications. Clinicians are allowed to prescribe countless drugs without first attesting to their competency to make an accurate diagnosis or provide care in the event of a complication. There is no reason why clinicians willing to provide medication abortion care should be trusted any less.

17. In short, this restriction is neither motivated nor supported by science.

18. At the same time, the Mifeprex REMS causes significant harm to patients. When a woman seeks a medication abortion and her clinician cannot provide her with timely care because of the REMS, at best, she will be forced to delay her abortion while she makes an additional, medically unnecessary trip to another

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[27] 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. D.

~~health care facility that has the medication on hand. At worst, she will be unable to obtain abortion care at all.~~

~~19. A woman whose abortion is delayed by the REMS is exposed to medical risks and psychological burdens that she otherwise would not face, and bears the sometimes prohibitive costs of travel to another health care facility. Making this additional trip—which may necessitate additional child care, additional time off work, and significant transportation expenses—also compromises some women's ability to keep their abortions confidential, with dangerous consequences for women in abusive relationships and young women with abusive parents.~~

~~20. Women in the most rural and medically underserved areas of the country—such as the island of Kaua'i, where Plaintiff Graham Chelius's patients live a flight away from the nearest abortion provider—experience particular harm. Put simply, the Mifeprex REMS makes health care less safe and more costly for rural women.~~

~~21. In *Whole Woman's Health v. Hellerstedt*, 136 S. Ct. 2292 (2016), *as revised* (June 27, 2016), the U.S. Supreme Court held that an abortion restriction purportedly designed to protect patient health and safety must actually do so, and the medical benefit must outweigh the burden on patient access, or else the law is constitutionally invalid. The Mifeprex REMS cannot survive this standard. To the contrary, the REMS *harms* patient health by delaying or preventing women's~~

~~access to timely medication abortion care and forcing some patients to carry a pregnancy to term against their will.~~

JURISDICTION AND VENUE

~~3.~~ This Court has subject matter jurisdiction over Plaintiffs' federal claims under Article III of the Constitution and 28 U.S.C. § 1331, as a civil action arising under the laws of the United States; 28 U.S.C. § 1346(a)(2), as a civil action against the federal government; 28 U.S.C. § 1343(a)(4), as a civil action to secure equitable or other relief under any Act of Congress providing for the protection of civil rights; and 5 U.S.C. § 702, as a civil action seeking judicial review of a final agency action.

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~~4.~~ Plaintiffs' action for declaratory and injunctive relief is authorized by 28 U.S.C. §§ 2201, 2202, and 1361, Federal Rules of Civil Procedure 57 and 65, and by the inherent equitable powers of this Court.

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22.

~~5.~~ There exists an actual and justiciable controversy between Plaintiffs and Defendants requiring resolution by this Court. Plaintiffs have no adequate remedy at law.

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~~6.~~ This Court has authority to award costs and attorneys' fees under 28 U.S.C. § 2412.

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~~22.~~25. Venue is proper in the District of Hawai‘i pursuant to 28 U.S.C. §§ 1391(b) and (e)(1), and 1402(a)(1), because this is a civil action in which Defendants are an agency, or officers of an agency, of the United States, because a substantial part of the events or omissions giving rise to this action occurred in the District, and because Plaintiff Chelius resides in the District.

PARTIES

A. Plaintiffs

~~23.~~26. Plaintiff Graham T. Chelius, M.D., is a board-certified family medicine physician with a focus in obstetrics. He ~~is the Chief Medical Officer~~ works for the Hawaii Health Systems Corporation’s Kaua‘i Region, which includes Kauai Veterans Memorial Hospital in Waimea, Kaua‘i, on the western side of the island (“Kauai Veterans”) and Samuel Mahelona Memorial Hospital in Kapa‘a, Kaua‘i, on the eastern side of the island. Dr. Chelius previously served as the Chief Medical Officer and Chief of Staff for the Hawaii Health Systems Corporation’s Kaua‘i Region. Over the past decade, he has delivered ~~more than 800~~well over a thousand babies on an island of ~~just over~~approximately ~~65~~74,000 people. Dr. Chelius brings this lawsuit solely in his individual capacity and does not speak on behalf of the Hawaii Health Systems Corporation. Dr. Chelius is a resident of the State of Hawai‘i.

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~~24.~~27. ~~As described *infra*, the~~The ~~Mifeprex~~ mifepristone REMS ~~prevents~~ undermines Dr. Chelius's relationship with and counseling of ~~from providing mifepristone to~~ his patients who use mifepristone, and jeopardizes his patients' privacy and safety. He sues on his own behalf and on behalf of his patients.

~~25.~~28. Plaintiff Society of Family Planning ("SFP") is a non-profit corporation with staff locations throughout the United States, ~~located in Philadelphia, Pennsylvania, and~~ incorporated in the state of ~~Pennsylvania~~Illinois. SFP is a national member association of clinicians, scholars, and partners united around advancing just and equitable abortion and contraception, informed by science. Membership in SFP is open to individuals who are in good professional standing and have a demonstrated interest in conducting or leveraging family planning research. ~~researchers with expertise in family planning. Membership in SFP is open to qualified individuals who are in good professional standing and have an interest in family planning demonstrated through post-doctoral training, a substantial clinical or laboratory practice, and academic presentations and publications within the field.~~ Since its incorporation in 2005, SFP's membership has grown to ~~nearly 800~~over 1,400 ~~fellows~~ members based primarily in the United States. Its members are trained in obstetrics and gynecology, internal medicine, family medicine, pediatrics/adolescent medicine, ~~and~~ public health, demography, nursing, epidemiology, and ~~among~~ other specialties. ~~SFP also has Ph.D. members,~~

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~~including social scientists, epidemiologists, demographers, and nurse researchers.~~ SFP works to advance sexual and reproductive health by providing evidence-based insight to improve clinical care in the areas of contraception and abortion. SFP also seeks to cultivate a collaborative and supportive environment to foster scholarly activity and leadership in the areas of reproductive health and family planning.

~~26.~~29. ~~As described *infra*,~~ SFP has members who are prevented from providing mifepristone to their patients because of the ~~Mifeprex~~ REMS. The REMS also impedes some of SFP's members from engaging in research and publication relating to mifepristone; undermines some of SFP's members' relationships with and counseling of their patients; jeopardizes the privacy and safety of some of SFP's members' patients; and prevents some of SFP's members' patients from using telemedicine to obtain mifepristone. SFP sues on behalf of its members and ~~its members'~~their patients.

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~~27.~~30. The California Academy of Family Physicians ("CAFP") is a non-profit professional association located in San Francisco, California. With ~~more than~~nearly 11~~9~~,000 family physician, family medicine resident, and medical student members, CAFP is the largest primary care medical society in California and the largest chapter of the American Academy of Family Physicians. Since 1948, it has engaged in advocacy and education to help family physicians improve their practices and expand access to high-quality and cost-effective patient care in California. To

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that end, CAFP offers affordable, evidence-based continuing medical education, provides cost-saving practice management resources, and fosters opportunities to promote the family medicine specialty and ensure a strong and healthy primary care pipeline. CAFP brings this lawsuit as an individual chapter and not as a representative of the American Academy of Family Physicians.

~~28.~~31. ~~As described *infra*,~~ CAFP has members who are prevented from providing mifepristone to their patients because of the mifepristone REMS. The REMS also impedes some of CAFP's members from engaging in research and publication relating to mifepristone; undermines some of CAFP's members' relationships with and counseling of their patients; jeopardizes the privacy and safety of some of CAFP's members' patients; and prevents some of CAFP's members' patients from using telemedicine to obtain mifepristone. ~~has members who are prevented from providing mifepristone to their patients because of the Mifeprex REMS.~~ CAFP sues on behalf of its members and ~~its members'~~their patients.

~~29. Pharmacists Planning Services Inc. ("PPSI") is a non-profit corporation located in San Rafael, California, and incorporated in the state of California. It has hundreds of independent pharmacist and pharmacy members across the country, including in Alaska, Arizona, Arkansas, California, Colorado, Delaware, Florida, Georgia, Hawai'i, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana,~~

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~~North Carolina, North Dakota, Nebraska, Nevada, New Jersey, New Mexico, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, and Wisconsin.~~

~~30. PPSI is involved in arranging and conducting certified continuing education programs for pharmacists, advocating on behalf of independent pharmacists before the California State Board of Pharmacy and other regulatory bodies, advising its members of developments of interest or concern to health care professionals, promoting public health concerns, and organizing campaigns and programs on health issues for consumers, pharmacists, and other health care professionals.~~

~~31. Because the Mifeprex REMS prohibits the sale of Mifeprex at retail pharmacies, PPSI's members—all of whom are pharmacists or pharmacies—are uniformly prevented from stocking and dispensing mifepristone. PPSI sues on behalf of its members and its members' patients.~~

B. Defendants

32. Defendant ~~Don J. Wright~~Xavier Becerra, J.D., ~~M.D., M.P.H.~~, who is being sued in his official capacity only, is the Acting Secretary of the United States Department of Health and Human Services ("HHS") and is responsible for administering and enforcing the FDCA. In particular, the Secretary is responsible for determining, in consultation with the office responsible for reviewing a drug and

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the office responsible for post-approval safety with respect to a drug, whether a REMS "is necessary to ensure that the benefits of the drug outweigh the risks of the drug . . . ." 21 U.S.C. § 355-1(a)(1). The Secretary may also, in consultation with the office responsible for reviewing the drug and the office responsible for post-approval safety with respect to the drug, require that any REMS include such ETASU as are necessary based on the drug's "inherent toxicity or potential harmfulness." *Id.* § 355-1(f)(1). Defendant ~~Wright~~ Becerra maintains an office in Washington, D.C.

33. Defendant FDA is an agency of the United States Government within HHS with offices in Washington, D.C., and Silver Spring, Maryland. The Secretary of HHS has delegated to ~~the~~ FDA the authority to administer the relevant provisions of the FDCA.

34. Defendant ~~Scott Gottlieb~~Robert M. Califf, M.D., who is being sued in his official capacity only, is the Commissioner of Food and Drugs and is responsible for supervising the activities of ~~the~~ FDA, including with regard to the imposition or removal of a REMS. Defendant ~~Gottlieb~~ Califf maintains offices in Washington, D.C., and Silver Spring, Maryland.

STATUTORY FRAMEWORK

A. FDA Approval Process for New Drugs

35. Before a drug can be marketed in the United States, the drug's sponsor must submit a new drug application ("NDA") to ~~the~~ FDA. If the NDA demonstrates that the drug is safe and effective, ~~the~~ FDA will approve it.

36. According to ~~the~~ FDA's website, this approval process incorporates three elements: *First*, "[a]nalysis of the target condition and available treatments," under which the Agency's reviewers

> analyze the condition or illness for which the drug is intended and evaluate the current treatment landscape, which provide the context for weighing the drug's risks and benefits. For example a drug intended to treat patients with a life-threatening disease for which no other therapy exists may be considered to have benefits that outweigh the risks even if those risks would be considered unacceptable for a condition that is not life-threatening.[28]

Second, ~~the~~ FDA performs an "[a]ssessment of benefits and risks from clinical data." ~~The~~ FDA explains that, "[g]enerally, the agency expects that the drug maker will submit results from two well-designed clinical trials," although "[i]n certain cases . . . convincing evidence from one clinical trial may be enough. Evidence that the drug will benefit the target population should outweigh any risks and uncertainties."[29] *Third*, ~~the~~ FDA considers "[s]trategies for managing risks." The Agency notes: "All

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[28] ~~U.S. Food & Drug Admin., *Development & Approval Process (Drugs)*,~~ U.S. Food & Drug Admin., ~~*available at*~~ https://www.fda.gov/drugs/developmentApprovalProcess/default.htm (last ~~visited~~ updated ~~Sept. 30~~ Aug. 8, 2022~~2017~~).

[29] *Id.*

drugs have risks. Risk management strategies include an FDA-approved drug label, which clearly describes the drug's benefits and risks, and how the risks can be detected and managed. Sometimes, more effort is needed to manage risks. In these cases, a drug maker may need to implement a Risk Management and Mitigation Strategy (REMS)."[30]

37. Based on this review, the Agency either: (1) approves the drug; (2) informs the sponsor that the drug is likely to be approved once certain deficiencies in the NDA are resolved; or (3) indicates that approval cannot be obtained without substantial additional data.

38. The Agency follows a similar process in evaluating a *supplemental* NDA, in which a drug sponsor requests approval to make changes to the labeling of a previously approved drug, or to market the drug for a new indication.

39. ~~The~~ FDA has authority under Section 506 of the FDCA (codified at 21 U.S.C. § 356) and its "Subpart H" regulations (21 C.F.R. §§ 314.500–560) to expedite approval of a new drug if it is a "promising therap[y] that treat[s] a serious or life-threatening condition and provide[s] therapeutic benefit over available therapies."[31]

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[30] *Id.*

[31] *Id.*

40. The Agency can condition approval for an NDA on the adoption of certain safety elements (*i.e.*, ETASU), such as a restricted distribution scheme. Until 2007, ~~the~~ FDA's primary authority to impose such elements was derived from the Subpart H regulations. However, this authority was effectively replaced by the REMS statute, described below, which was adopted as part of the Food and Drug Administration Amendments Act of 2007 ("FDA Amendments Act").

41. Section 909 of the FDA Amendments Act states that all drugs licensed before March 2008 that were approved under Subpart H with ETASU would be automatically deemed to have an approved REMS in place. The Agency can, however, impose a REMS for any drug that fits the statutory criteria, not only those drugs originally approved under Subpart H.

B. The REMS Statute

42. The FDA Amendments Act amended the FDCA to add a new section 505-1 (codified at 21 U.S.C. § 355-1) authorizing the Secretary of HHS, in consultation with ~~the~~ FDA's Office of New Drugs and the Office of Surveillance and Epidemiology, to impose a REMS if—and only if—"necessary to ensure that the benefits of a drug outweigh [its] risks . . . ." 21 U.S.C. § 355-1(a)(1).

43. To determine whether a REMS is necessary, the Secretary must consider six factors: (1) "[t]he estimated size of the population likely to use the drug involved," (2) "[t]he seriousness of the disease or condition that is to be treated with the drug,"

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(3) "[t]he expected benefit of the drug with respect to such disease or condition," (4) "[t]he expected or actual duration of treatment with the drug," (5) "[t]he seriousness of any known or potential adverse events that may be related to the drug and the background incidence [*i.e.*, frequency] of such events in the population likely to use the drug," and (6) "[w]hether the drug is a new molecular entity." *Id.*

44. A REMS may include any or all of the following: a medication guide and/or patient package insert; a communication plan; and elements to assure safe usage (*i.e.*, ETASU), such as a restricted distribution scheme. *Id.* § 355-1(e)-(f).

45. ETASU are the most restrictive and burdensome type of REMS. The FDCA authorizes the Agency to impose ETASU only where "necessary to assure safe use of the drug, *because of its inherent toxicity or potential harmfulness*," *id.* § 355-1(f)(1) (emphasis added), and only if the drug is "associated with a serious adverse drug experience," *id.* § 355-1(f)(1)(A), which is defined by statute as an adverse event associated with use of the drug that results in death, the immediate risk of death, inpatient hospitalization or prolonging existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly or birth defect, or a medical or surgical intervention to prevent these outcomes, *id.* § 355-1(b)(4).

46. Moreover, ~~the~~ FDA may impose ETASU only where "required as part of [a] strategy *to mitigate a specific serious risk*"—*i.e.*, a "serious adverse drug

experience," *id.* § 355-1(b)(5)—"listed in the labeling of the drug," and the risk must be sufficiently great that ~~the~~ FDA would not approve, or would withdraw approval for, the drug absent the ETASU. *Id.* § 355-1(f)(1)(A) (emphasis added).

47. Congress imposed several additional requirements to ensure that ~~the~~ FDA appropriately balances such an inherently toxic drug's benefits against its "serious risks." The ETASU requirements must "be *commensurate* with the specific serious risk[s]" listed in the drug's labeling, and may "not be *unduly burdensome* on patient access to the drug, considering in particular . . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)." *Id.* §§ 355-1(f)(2)(A), (C) (emphases added). In addition, "to the extent practicable, so as to minimize the burden on the health care delivery system," ETASU must "conform with elements to assure safe use for other drugs with similar, serious risks." *Id.* § 355-1(f)(2)(D).

48. A modification or removal of a REMS may be initiated by a "responsible person" (*i.e.*, the drug's sponsor) or by the Secretary of HHS, who may "require a responsible person to submit a proposed modification to the strategy." *Id.* §§ 355-1(g)(4)(A), (B).

49. In addition, the Secretary of HHS must "periodically evaluate, for 1 or more drugs, the [ETASU] to assess whether the elements (i) assure safe use of the drug; (ii) are not unduly burdensome on patient access to the drug; and (iii) to the extent

practicable, minimize the burden on the health care delivery system." *Id.* § 355-1(f)(5)(B). Then, "considering such input and evaluations," the Aagency must "modify [ETASU] for 1 or more drugs as appropriate." *Id.* § 355-1(f)(5)(C).

FACTUAL ALLEGATIONS

A. ~~Mifeprex~~ Mifepristone Regimen and Safety Record

50. The current FDA-approved regimen for the medical termination of early pregnancy involves two drugs: (1) *mifepristone* (under the brand name Mifeprex or as a generic), which interrupts early pregnancy by blocking the effect of progesterone, a hormone necessary to maintain a pregnancy, and (2) *misoprostol* (under the brand name Cytotec® or as a generic), which causes uterine contractions that expel the pregnancy from the uterus. ~~The~~ FDA expressly authorizes misoprostol for use as part of this regimen although misoprostol's own marketing approval is only for the prevention of gastric ulcers.

51. ~~The~~ FDA has approved the use of this regimen through 70 days (*i.e.*, 10 weeks) of pregnancy, when the overwhelming majority (~~approximately~~ more than 80%) of abortions occur.[32]

[32] ~~Tara C. Jatlaoui~~Katherine Kortsmit et. al., Ctrs. for Disease Control & Prevention, *Abortion Surveillance – United States, 2020~~13~~*, ~~65~~ 71 Morbidity & Mortality Weekly Report ~~12, 26, 28~~1

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~~52. Taken alone, misoprostol also acts as an abortifacient—but it is less effective and causes more severe side effects than the Mifeprex/misoprostol regimen. Nevertheless, unlike Mifeprex, misoprostol is not subject to a REMS, and thus patients may obtain it from a pharmacy with a prescription. As a result, some patients receive the two drugs approved for a medication abortion in two different places: the first (Mifeprex) at a clinic, doctor's office, or hospital, as required by the REMS; the second (misoprostol) at a local pharmacy or via a mail-order pharmacy.~~

~~53.~~52. ~~Under the current~~The FDA-approved regimen for mifepristone states that~~,~~ the patient initiates the abortion by taking one 200 mg tablet of ~~Mifeprex~~ mifepristone in a single oral dose on day one, and then 24–48 hours later~~. Then, 24-48 hours later, she~~ takes four 200 mcg tablets of misoprostol buccally (*i.e.*, by placing two pills in each cheek pouch—the area between the cheek and the gums—for 30 minutes and then swallowing any remnants with water or another liquid). The FDA-approved labeling does not specify where ~~the~~ patients should be located when ~~she~~ they take~~s~~ either medication. Most ~~women~~ people will expel the pregnancy within 2 to 24 hours after taking the misoprostol. The patient is instructed to follow up with their health care provider approximately 7 to 14 days later to confirm that

(Nov. 25, ~~2016~~2022), https://www.cdc.gov/mmwr/volumes/71/ss/ss7110a1.htm~~https://www.cdc.gov/mmwr/volumes/65/ss/pdfs/ss6512.pdf~~.

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the termination of pregnancy was successful, but the FDA labeling no longer anticipates that this follow-up evaluation will occur in-person.

~~54.~~53. Like all medication labels, the ~~Mifeprex~~ mifepristone labeling warns about potential risks associated with the drug. Its labeling lists as risks "serious and sometimes fatal infections or bleeding."[33]

54. As ~~the~~ FDA explained in its Summary Review Memorandum for Mifeprex in March 2016, which evaluated changes to the Mifeprex labeling and REMS, "~~[~~t~~]~~here have been approximately 2.5 million uses of Mifeprex by U.S. women since the drug's approval in 2000."[34] During that time, ~~the~~ FDA noted, medication abortion "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."[35] 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."[36]

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[33] AR 0383–84. ~~Mifeprex Label 1, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf (last visited Oct. 1, 2017) [hereinafter "Mifeprex Label"].~~

[34] AR 0422. ~~2016 Summary Review, *supra* note 9, Ex. C, at 10.~~

[35] ~~2016 Medical Review, *supra* note 1, Ex. A, at 12.~~AR 0539.

[36] ~~U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Mifeprex Risk Assessment and Risk Mitigation Review(s): REMS Modification Memorandum 3 (Mar. 29,~~

55. Mifepristone is also FDA-approved under the brand name Korlym® in 300 mg tablets for *daily use* by patients with endogenous Cushing's syndrome to treat high blood sugar caused by high cortisol levels in the blood. Korlym is available only from a specialty pharmacy, but it is *not* subject to a REMS. A patient's doctor submits a patient enrollment form and prescription for Korlym to a specialty pharmacy, which delivers the drug to the patient's home. The patient is then responsible for taking one to four pills (300 mg to 1200 mg, 1.5 to 6 times the recommended dose for Mifeprex) daily at home according to their prescription. In its 2016 Medical Review of Mifeprex, the Agency observed that "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."[37]

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~~55.~~56. Mifepristone is also frequently prescribed with misoprostol as part of a regimen for medical management of early pregnancy loss. SFP, ACOG, and other leading medical associations recommend that clinicians prescribing medications to treat a miscarriage (*i.e.*, to completely evacuate the patient's uterus) utilize the combined mifepristone-misoprostol regimen whenever mifepristone is available.

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~~2016) [hereinafter "2016 REMS Modification Memorandum"], attached hereto as Ex. E.~~AR 0681.

[37] ~~2016 Medical Review, *supra* note 1, Ex. A, at 10.~~AR 0537.

But, as ACOG notes in its Practice Bulletin on Early Pregnancy Loss, while "[t]he addition of a dose of mifepristone (200 mg orally) 24 hours before misoprostol administration may significantly improve treatment efficacy . . . the availability of mifepristone is limited by the [FDA]'s Risk Evaluation and Mitigation Strategy restrictions."[38]

B. FDA Approval of Mifeprex and Imposition of the REMS

1. Initial FDA Approval

~~56.~~57. Mifepristone was approved for the medical termination of early pregnancy in France and China in 1988; in the United Kingdom in 1991; in Sweden in 1992; and in numerous other European countries throughout the 1990s.

~~57.~~58. In March 1996, the Population Council, a non-profit organization based in the United States, sponsored an 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") for the manufacturing and marketing of the medication.

~~58.~~59. There were three historically-controlled clinical trials on the safety and efficacy of the Mifeprex and misoprostol regimen presented to ~~the~~ FDA as part of the original NDA application, together involving 4,000 women: two trials

[38] ACOG, Practice Bulletin No. 200: Early Pregnancy Loss (Nov. 2018), *available at* https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/11/early-pregnancy-loss.

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conducted in France, which were complete at the time of the application, and one then-ongoing trial in the United States for which summary data on serious adverse events were available. The Agency 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]."[39] As part of the NDA review, ~~the~~ 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); and (3) data on the drug's chemistry and marketing.

~~59.~~60. Four years later, i~~I~~n September 2000, ~~the~~ FDA granted final marketing approval for Mifeprex for use in combination with misoprostol for the termination of pregnancy up to 49 days.

~~60.~~61. Despite the strong findings on the safety and efficacy of Mifeprex from clinical trials and European post-market experience, and despite the fact that the approval process was not expedited, the A~~a~~gency approved Mifeprex under Subpart H (which provides for accelerated approval—though, in fact, this four-year process

[39] ~~Letter Denying Petition to Revoke Mifeprex Approval, *supra* note 3, Ex. B, at 8.~~AR 0863.

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was not expedited) and imposed ETASU—a restricted distribution system—as a condition of approval.

~~61.~~62. The ETASU imposed at the time of Mifeprex's original approval are substantively identical to the ETASU ~~the~~ that FDA renewed in 2011 and again in 2016, described in detail *infra*.

~~62.~~63. According to a report by the U.S. Government Accountability Office ("GAO"), ~~the~~ FDA stated that Mifeprex fit within the scope of Subpart H because unwanted pregnancy poses a risk of serious or life-threatening complications, Mifeprex terminates an unwanted pregnancy, and Mifeprex allows patients to avoid the risks incident to a surgical abortion procedure.[40] ~~The~~ FDA further stated that the restricted distribution scheme was necessary to ensure patient safety, and that approving Mifeprex under Subpart H would allow ~~the~~ FDA to impose comparable restrictions on any future generic mifepristone products.[41]

~~63.~~64. The Agency'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

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[40] U.S. Gov't Accountability Office, *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex*, GAO-08-751, 22 (Aug. 2008), *available at* http://www.gao.gov/new.items/d08751.pdf.

[41] *Id.* at n.41.

ETASU under Subpart H.[42] By comparison, there were 961 NDAs approved in the roughly thirteen years from January 1993 to September 2005.[43]

~~64.~~65. Though noting its objections, the Population Council agreed to the restrictions in September 2000, and Danco began distribution of Mifeprex in November 2000. The Population Council subsequently transferred ownership of the NDA to Danco.

2. 2008 and 2011 Imposition of the Mifeprex REMS

~~65.~~66. In a rule released in March 2008 pursuant to the FDA Amendments Act, the Agency identified Mifeprex as one of the drugs deemed to have an approved REMS in effect because it already had ETASU in place under Subpart H. Mifeprex continued to be distributed subject to the same restrictions under which it was originally approved.

~~66.~~67. In 2011, ~~the~~ FDA issued a new REMS for Mifeprex incorporating the same restrictions under which the drug was approved eleven years earlier. Specifically, the Mifeprex REMS approved in 2011 required three elements:

~~67.~~68. *First*, a Medication Guide to be dispensed with each Mifeprex prescription.

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[42] *Id.* at n.6, 27.

[43] U.S. Gov't Accountability Office, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49, 20 (Nov. 2006), *available at* http://www.gao.gov/new.items/d0749.pdf.

~~68.~~69. *Second*, the 2011 REMS included three types of ETASU (A, C, and D)~~.~~:

- ETASU A required~~s~~ clinicians to self-certify before they ~~may~~ could prescribe Mifeprex. ~~Under ETASU A, all health care providers who prescribe Mifeprex must be specially certified.~~ To be certified, the provider complete~~d~~s and faxe~~d~~s to the Mifeprex distributor a one-time Prescriber's Agreement, agreeing that they me~~e~~t the qualifications and ~~will~~ would follow the guidelines outlined in the Prescriber's Agreement. These guidelines require~~d~~ prescribers to attest that they ~~have~~ had the ability to date a pregnancy; ~~have~~ had the ability to diagnose an ectopic pregnancy; ~~have~~ had made plans for the patient to receive surgical abortion care in cases of incomplete abortion or severe bleeding, and to ensure the patient has access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and ~~have~~ had read and understood the prescribing information for Mifeprex. In addition, the prescriber ~~must~~ agree~~d~~ to provide the patient with the Medication Guide and Patient Agreement, give her an opportunity to read and discuss them, obtain her signature on the Patient Agreement, and then sign it as well; notify the manufacturer of any cases of incomplete abortion, hospitalization,

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transfusion, or other serious event; and record the unique serial number on each package of Mifeprex in each patient's record.

- ETASU C restricted~~s~~ where a patient ~~may~~ could receive Mifeprex once ~~it is~~ prescribed. Under ETASU C, Mifeprex ~~may~~ could be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a prescriber specially certified under ETASU A. Mifeprex ~~may~~ could not be dispensed through retail pharmacies.
- ETASU D placed~~s~~ additional requirements on the patient receiving Mifeprex. Under ETASU D, Mifeprex ~~may~~ could be dispensed only to a patient who ha~~s~~d completed and signed a Patient Agreement form, a copy of which ~~must~~ was required to be placed in her medical record, and who ~~has~~ had been provided a copy of the Medication Guide.

~~69.~~70. *Third*, an Implementation System, under which distributors agreed to ship the drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements; maintain secure and confidential records of shipments; and follow all distribution guidelines, including for storage, tracking, proof of delivery, and controlled returns.

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71. *Fourth*, as is typical for any REMS, the sponsor wa~~i~~s required to submit a REMS "assessment" to ~~the~~ FDA one year from the date of the initial approval of the REMS and every three years thereafter.

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3. 2016 Mifeprex Labeling Changes and REMS Assessment

a. Requested Changes to Mifeprex Label and REMS

~~70.~~72. Off-label use of drugs—*i.e.*, in accordance with prevailing clinical evidence, using a medication for a different indication or in a different regimen than that listed on ~~an~~ the FDA-approved labeling—is extremely common and widely accepted in the United States. Thus, shortly after ~~the~~ FDA approved Mifeprex in 2000, abortion providers started prescribing the evidence-based protocol (using 200 mg of mifepristone) rather than the regimen listed on the labeling (using 600 mg of mifepristone). However, after several states banned off-label use of mifepristone—forcing patients to use an outdated regimen that was less safe and less effective than prevailing practice—in May 2015, Danco submitted a supplemental NDA to ~~the~~ FDA proposing to update the labeling to reflect evidence-based practice across the country. In July 2015, Danco also submitted its statutorily required REMS assessment, proposing minor modifications to the REMS (primarily to ensure that the language used in the prescriber and patient agreement forms reflected the proposed changes to the labeling).

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~~71.~~73. This submission prompted a top-to-bottom review of the Mifeprex labeling and REMS by ~~the~~ FDA in 2015-2016. As part of that review, the Agency stated that it considered three letters submitted by more than 40 medical experts, researchers, advocacy groups, and professional associations—including Plaintiff SFP—who asked, *inter alia*, that the REMS be eliminated.

~~72.~~74. Other signatories requesting that ~~the~~ FDA eliminate the Mifeprex REMS included ~~the American Congress of Obstetricians and Gynecologists (“ACOG”)~~, the leading professional association of physicians specializing in the health care of women, which represents ~~58,000~~more than 60,000 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; and the Senior Research Demographer in the Office of Population Research at Princeton University.

~~73.~~75. The Agency’s March 2016 Cross Discipline Team Leader Review Memorandum for Mifeprex (“2016 Team Leader Review”), in a section entitled “Advocacy Group Communications,” noted:

> The Agency received three letters from representatives from academia and various professional organizations, including [ACOG], [APHA], the National Abortion

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> Federation (NAF), Ibis Reproductive Health and Gynuity [Health Projects]. 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*. (emphasis added).[44]

~~74.~~76. In ~~the~~ FDA's 2016 Medical Review, in a section entitled "Methods," the Agency further noted: "Articles were also cited in three letters sent to [Center for Drug Evaluation and Research] 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."[45]

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~~75.~~77. Director Woodcock also directly acknowledged receipt of the letter submitted by thirty professional and academic organizations, including Plaintiff

[44] ~~U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Cross Discipline Team Leader Review 25 (Mar. 29, 2016) [hereinafter "2016 Team Leader Review"], attached hereto as Ex. F.~~AR 0465.

[45] ~~2016 Medical Review, *supra* note 1, Ex. A, at 23.~~AR 0550.

SFP. In a February 25, 2016, letter addressed to the individual serving as the liaison for those groups, she wrote:

> Thank you for your letter dated February 4, 2016, to [then-Acting FDA Commissioner] Dr. Ostroff, Dr. Califf, and me with recommendations to lift the Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex (mifepristone), and to extend the indicated use of Mifeprex through a gestational age of 70 days. Dr. Ostroff has asked me to respond on behalf of the FDA because the Center for Drug Evaluation and Research is responsible for regulating all drugs, including mifepristone. Please share this response with your cosigners. In your letter, you strongly encouraged FDA to revise the mifepristone label and eliminate the REMS restrictions, especially the Elements to Assure Safe Use [ETASU] . . . . You also recommended not restricting the location where the patient should take these drugs . . . . Moreover, you proposed that any licensed health care provider should be able to prescribe mifepristone, and that it be available through pharmacies as well as provider offices. Your letter has been shared with the appropriate FDA staff and will be carefully reviewed.[46]

~~76.~~78. The letter submitted by Plaintiff SFP argued, *inter alia*:

> 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 and that serious complications are rare. The steady increase in use of medication abortion – now 23% of U.S. abortions – shows that many women prefer this

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[46] ~~Letter from Janet Woodcock, M.D., Ctr. for Drug Evaluation & Research, to Jessica Arons, J.D. (Feb. 25, 2016), attached hereto as Ex. G.~~ AR 1265.

> option, and that it has the ability to improve access to abortion, even in states with restrictive laws . . . . 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 . . . . As policy, advocacy, social science, research, and academic organizations, we ask the FDA to consider the substantial evidence presented in the [letter previously submitted by academic professionals and women's health non-profit organizations], 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, 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.[47]

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~~77.~~79. SFP's letter also explained in detail why the Mifeprex REMS with ETASU harms patient access to Mifeprex. In particular, SFP's letter stated that ETASU C, which ~~restricts~~ restricted where Mifeprex ~~may~~ could be dispensed, "significantly curtails mifepristone's potential to expand patient access to abortion care" because it "[is] a burden to providers and, therefore, deter[s] some health care providers from offering medication abortion."[48] They explained:

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> 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

[47] ~~Letter from SFP, *et al.*, to Stephen Ostroff, M.D., Robert M. Califf, M.D., & Janet Woodcock, M.D., 1 (Feb. 4, 2016) [hereinafter "SFP Letter to FDA"], attached hereto as Ex. H.~~AR 1254.

[48] ~~*Id.*, Ex. H, at 2.~~AR 1255.

> 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 . . . . [T]he majority of people who seek abortion care are already in difficult financial situations, and are disproportionately people of color. Costly and unnecessary visits to the doctor significantly increase financial and logistical burdens for these individuals and communities.[49]

~~78.~~80. SFP's letter explained why ETASU A, the Prescriber's Agreement, "is unnecessary for the safe dispensation of mifepristone," noting, *inter alia*, that "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."[50]

~~79.~~81. SFP and the other signatories further argued that the Prescriber's Agreement

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[49] ~~Id., Ex. H, at 2–3.~~AR 1255–56.

[50] ~~Id., Ex. H, at 3.~~AR 1256. According to ~~the~~ FDA, a "boxed" or "black box warning" "appears on a prescription drug's labeling and is designed to call attention to serious or life-threatening risks." U.S. Food & Drug Admin., Consumer Health Information, *A Guide to Drug Safety Terms at FDA* 2 (Nov. 2012), *available at* https://www.fda.gov/downloads/forconsumers/consumerupdates/ucm107976.pdf.

> 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.[51]

~~80.~~82. The letter also noted that "[t]he Prescriber's Agreement would be incompatible and unnecessary if there were an expanded distribution system."[52]

~~81.~~83. Finally, the letter requested that the Agency remove ETASU D, the Patient Agreement, which is "medically unnecessary and interferes with the clinician-patient relationship."[53]

b. FDA's 2016 Approval of Revised Label

~~82.~~84. ~~The~~ FDA adopted nearly all of Danco's proposed labeling changes (discussed *supra* at ¶ ~~76~~72), including reducing the recommended dosage of

[51] ~~SFP Letter to FDA, *supra* note 29, Ex. H, at 3.~~AR 1256.

[52] *Id.*

[53] ~~Id. at 4.~~AR 1257.

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mifepristone from three 200 mg tablets to one 200 mg tablet and removing the reference to the patient's follow-up assessment—to assure completion of the abortion seven to fourteen days after taking the mifepristone—as an in-person examination.

~~83.~~85. ~~The~~ FDA also approved two changes regarding where the ~~woman~~ patient takes the mifepristone and misoprostol. First, the labeling no longer ~~states~~ stated that the ~~woman~~ patient takes the ~~Mifeprex~~ mifepristone and misoprostol "at [their] provider's office." Rather, although health care providers ~~must~~ were still required to *dispense* the Mifeprex only in certain medical facilities according to the REMS, the ~~new~~ updated labeling ~~does not~~no longer specified~~y~~ where ~~she~~ they *take~~s~~* the pill; it simply ~~states~~ stated that the ~~woman~~ patient takes the ~~Mifeprex~~ mifepristone in a single oral dose on "Day One," and ~~that she~~then takes four tablets of misoprostol by the buccal route 24-48 hours later.[54] The labeling advises the health care provider to "discuss with the patient an appropriate location for her to be when she takes the misoprostol, taking into account that expulsion [*i.e.*, the miscarriage] could begin within 2 hours of administration."[55]

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[54] ~~Mifeprex Label, *supra* note 16, at 3.~~AR 0385.

[55] *Id.*

86. In addition, the ~~new~~ labeling ~~clarifies~~ clarified that ~~Mifeprex~~ mifepristone can be safely used through 70 days of pregnancy (rather than 49).[56] The Agency concluded in its 2016 Medical Review that, based on the scientific evidence, "[m]edical termination of pregnancies through 70 days gestation is safe and effective and should be approved."[57]

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c. FDA's 2016 Reauthorization of the REMS

~~84.~~87. As part of its review of the proposed labeling changes, the Agency undertook to "assess[] the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks."[58] This assessment was conducted by a multidisciplinary reviewing team and elevated to the Commissioner of ~~the~~ FDA, a political appointee—Defendant Robert Califf, who would later also helm FDA at the time of the 2023 REMS updates~~,~~ —who gave specific feedback on proposed changes to the Mifeprex REMS.

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[56] AR 0383, 0384, 0391, 0399. ~~*Id.* at 1.~~

[57] AR 0548. ~~2016 Medical Review, *supra* note 1, Ex. A, at 21.~~

[58] AR 0375. ~~U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Supplement Approval Letter for Mifeprex 2 (Mar. 29, 2016) [hereinafter "2016 Supplement Approval Letter"], attached hereto as Ex. I.~~

~~85.~~88. FDA reviewers met on January 15, 2016, "to discuss proposed revisions to the REMS," and the Agency's review process was documented in detail in at least seven internal memoranda (attached ~~here~~ to Plaintiffs' original complaint as Exhibits A, C-F, J-K). In evaluating each element of the REMS, the Agency considered, *inter alia*, "safety data gathered over the past 16 years since approval, and information ~~about~~regarding current clinical practice."[59]

~~86.~~89. Following this comprehensive review, the Agency "determined that a REMS continues to be necessary to ensure the safe use of Mifeprex," and reauthorized the REMS program, including all of the ETASU, with only minor modifications.[60]

~~87.~~90. The reauthorization of the REMS in March 2016 constituted a final agency action. It marked the consummation of the Agency's decision-making process and was a decision from which legal consequences flowed.

~~88.~~91. The Agency made the following modifications to the REMS: (1) revisions to the language in the Prescriber's Agreement form; (2) removal of the Medication Guide as a REMS element; (3) updating of the REMS goals to reflect

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[59] AR 0702.~~U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Mifeprex Risk Assessment and Risk Mitigation Review(s): REMS Modification Review 5 (Mar. 29, 2016), attached hereto as Ex. J.~~

[60] ~~U.S. Food & Drug Admin., Mifeprex (mifepristone) Information, *available at* https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323.htm (last visited Sept. 30, 2017).~~AR 0849.

these changes; and (4) removal of the additional adverse event reporting requirements, other than with respect to deaths.[61] The stated goal of the ~~current~~ 2016 Mifeprex REMS program ~~is~~ was "to mitigate the risk of serious complications associated with Mifeprex by: (a) Requiring health care providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program[,] (b) Ensuring that Mifeprex is only dispensed in certain health-care settings by or under the supervision of a certified prescriber[,] [and] (c) Informing patients about the risk of serious complications associated with Mifprex."[62]

~~89.~~92. The Agency's multidisciplinary team of reviewers had also recommended eliminating ETASU D, the Patient Agreement form, because they concluded that it was no longer necessary. As Director Woodcock explained in a March 28, 2016, internal memorandum, Agency staff "found that the information contained in the Patient Agreement Form [required by the REMS] is generally duplicative of information in the Medication Guide and of information and counseling provided to patients under standard informed consent practices for

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[61] AR 0680–81; *see also* AR 0688. ~~2016 REMS Modification Memorandum, *supra* note 19, Ex. E, at 2 (listing changes), 4 (discussing retention of ETASU D); *see also* U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, 020687Orig1s020, Mifeprex Risk Assessment and Risk Mitigation Review(s): Addendum to REMS Modification Review 5 (Mar. 29, 2016), attached hereto as Ex. K (discussing modifications to the reporting requirement).~~

[62] AR 0404. ~~Current Mifeprex REMS, *supra* note 6, at 1.~~

medical care and under professional practice guidelines."[63] Agency reviewers observed that "[i]t is standard of care for patients undergoing pregnancy termination to undergo extensive counseling and informed consent,"[64] and noted that ~~the~~ "FDA has removed REMS requirements in other programs based on the integration of the REMS safe use condition into clinical practice."[65] The Agency's 2016 Summary Review "concur[red] 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*."[66]

~~90.~~93. However, "[a]fter being briefed on the planned changes to the NDA that the Center [for Drug Evaluation and Research] was considering, the Commissioner [of ~~the~~ FDA] . . . requested that the Patient Agreement Form be retained as an element of the REMS."[67] Therefore, Director Woodcock "asked [Agency staff] to include a Patient Agreement Form in the REMS for Mifeprex," which they did.[68]

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[63] AR 0674.~~Woodcock Patient Agreement Memo, *supra* note 10, Ex. D, at 1.~~

[64] AR 0437.~~2016 Summary Review, *supra* note 9, Ex. C, at 25.~~

[65] AR 0465.~~2016 Team Leader Review, *supra* note 26, Ex. F, at 25.~~

[66] AR 0437.~~2016 Summary Review, *supra* note 9, Ex. C, at 25 (emphasis added).~~

[67] AR 0674.~~Woodcock Patient Agreement Memo, *supra* note 10, Ex. D, at 1.~~

[68] *Id.*~~, Ex. D~~.

94. It is extremely rare that the FDA Commissioner, a political appointee, would weigh in on a REMS assessment. This unusual interference is consistent with the Agency's conduct denying the application to make Plan B® (commonly known as "the morning after pill"), which is used to prevent pregnancy, available over-the-counter with no age restrictions—where the U.S. District Court for the Eastern District of New York found "overwhelming evidence of political pressure underlying the agency's actions." *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 166 (E.D.N.Y. 2013) (finding that FDA did not have authority to mandate point-of-sale restrictions on levonorgestrel-based emergency contraception given the scientific data demonstrating that adolescents could safely use Plan B).

d. Events Post-Dating Plaintiffs' Filing

95. In October 2017, Plaintiffs filed the instant matter.

96. In 2019, FDA approved a generic version of mifepristone with substantively identical labeling, and established a single, shared system REMS encompassing both Mifeprex and the generic version that is substantively identical to the REMS approved for Mifeprex in 2016. The single, shared system REMS is known as the Mifepristone REMS Program.[69]

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[69] 2023 REMS Review, *supra* note 8, at 6.

97. In March 2020, in response to the COVID-19 pandemic, Defendants FDA and HHS took extraordinary measures to promote the use of telemedicine and reduce the need for in-person health care visits, in order to mitigate viral exposure risks. For instance, FDA issued guidance declaring its intention not to enforce REMS requirements for in-person laboratory testing for the duration of the public health emergency, and the Secretary of HHS activated an emergency exception allowing health care providers to prescribe controlled substances, including opioids, via telemedicine without first conducting an in-person examination.[70]

98. Leading medical associations and health care providers asked FDA to likewise exercise enforcement guidance with respect to the in-person dispensing ETASU for mifepristone.[71] But FDA left that restriction in place, offering no explanation for its constructive denial—and continuing its singular treatment of mifepristone.

99. In May 2020, ACOG led a coalition of plaintiffs in a challenge to the mifepristone in-person dispensing ETASU in the U.S. District Court for the District

[70] U.S. Food & Drug Admin., Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency: Guidance for Industry and Health Care Professionals (Mar. 2020), https://www.fda.gov/media/136317/download; *COVID-19 Information Page, Telemedicine*, U.S. Drug Enf't Admin., https://www.deadiversion.usdoj.gov/coronavirus.html#TELE (last visited Mar. 30, 2023).

[71] *See, e.g.*, Letter from Maureen G. Phipps, MD, MPH, FACOG, Judette Louis, MD, MPH, and Matt J. Granato, LLM, MBA, to Stephen M. Hahn, MD (Apr. 20, 2020), attached hereto as Suppl. Ex. F.

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of Maryland, resulting in a preliminary injunction that blocked enforcement of this requirement for the six months the injunction was in place, and for the first time enabled mifepristone patients to obtain their medication from a mail-order pharmacy. *ACOG v. FDA*, 472 F. Supp. 3d 183 (D. Md. 2020), *stayed*, 141 S. Ct. 578 (2021) (mem.).

100. On April 12, 2021, FDA announced that it intended to exercise enforcement discretion for the remainder of the COVID-19 Public Health Emergency with respect to the mifepristone in-person dispensing requirement.[72]

101. On April 16, 2021, Plaintiffs moved for summary judgment in the instant matter. Shortly thereafter, FDA informed Plaintiffs that it was comprehensively reviewing the mifepristone REMS. On the condition that FDA would also "review any relevant data and evidence submitted by the Plaintiffs," Joint Mot. Stay 2 (ECF 148), the parties jointly moved for a stay, which this Court granted on May 7, 2021. As FDA explains in its Frequently Asked Questions for mifepristone, this litigation was the catalyst for its REMS Review: "The agency's comprehensive review of the Mifepristone REMS Program, which led to the

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[72] 2023 REMS Review, *supra* note 8, at 6.

agency's December 16, 2021, decision that a modification is required, was related to the litigation in *Chelius v. Becerra*."[73]

102. In May 2021, FDA approved a supplemental new drug application seeking to modify the Patient Agreement Form for mifepristone to reflect gender-neutral language.[74]

103. In August and September 2021, Plaintiffs submitted to FDA two letters containing evidence demonstrating that the mifepristone REMS is medically unnecessary and burdensome on patients (especially patients who face difficulties accessing health care) and on the health care delivery system itself. For instance, Plaintiffs' letters included:

- Statements opposing the mifepristone REMS by other leading medical associations, including the American Medical Association ("AMA"), ACOG, and the American Academy of Family Physicians ("AAFP").[75]
- Specific examples of other medications posing risks greater than or comparable to that of mifepristone that are *not* subject to a REMS.[76]

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[73] *Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation*, U.S. Food & Drug Admin. (last updated Jan. 4, 2023), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation (answer to question 29, under "Litigation and Other Legal Issues"; *accord id.* (answer to question 35, under "The January 2023 REMS Modification").

[74] 2023 REMS Review, *supra* note 8, at 5.

[75] *Chelius* Plaintiffs' Letter, *supra* note 10, at 1.

[76] *Id.* at 3.

- A study abstract showing that after Canada eliminated its restrictions on mifepristone in 2017 to allow normal prescribing, medication abortion remained extremely safe, with a major complication rate of 0.33%.[77]

- Sworn testimony from seven physicians in different states detailing how the mifepristone REMS prevented or substantially delayed them and other doctors they know from prescribing mifepristone, impeding patients' access. For instance, Dr. Joey Banks cited specific examples of physicians who have told her that the reason they do not provide mifepristone is because they are "worried" about being placed "on a list of abortion providers."[78] Dr. Charisse Loder explained how it took years to make mifepristone available at the University of Michigan's Women's Clinic, including because of "concerns that the University would face legal liability if clinicians who were not acting pursuant to a REMS prescriber agreement prescribed this drug," which a special taskforce spent "many meetings" discussing.[79] Dr. Jane Roe discussed how the patient agreement "actively *undermines* my informed consent process by forcing me to discuss with my patients information that is inconsistent with my clinical approach and increasingly out-of-step with the research on Mifeprex as science moves forward," for instance by requiring patients to attest that they are having an abortion even if they are in fact using the medication to treat a miscarriage.[80]

- An analysis from a leading national expert in poverty and women's welfare regarding how the REMS reduces patients' access to mifepristone, particularly for patients with lower incomes and patients living in rural and medically underserved areas.

104. Other leading medical professional associations, such as ACOG, also submitted their own letters opposing the REMS. For instance, in a letter submitted

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[77] *Id.* at 2.

[78] *Id.* at App. 040–41.

[79] *Id.* at App. 066–69.

[80] *Id.* at App. 084–85 (emphasis in original).

on October 6, 2021, ACOG noted that "[t]he REMS and ETASU requirements for mifepristone are inconsistent with those for other medications with similar safety profiles, and create barriers to access without demonstrated improvements to patient safety or outcomes."[81]

105. FDA's 2021 REMS Review memorandum states that the agency's review encompassed a search of published literature through July 26, 2021, as well as "safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants [*i.e.*, Danco and GenBioPro, which manufactures the generic]." FDA's "review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below."[82]

106. In fact, FDA expressly omitted from its analysis much of the data and evidence provided by the *Chelius* Plaintiffs. FDA refused to consider, *inter alia*, "[i]nformation from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, *even if the study assessed REMS ETASUs*," "[o]pinions,

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[81] Letter from Maureen G. Phipps, MD, MPH, FACOG, to Janet Woodcock, MD (Oct. 6, 2021), attached hereto as Suppl. Ex. G.

[82] 2021 REMS Review, *supra* note 9, at 4.

commentaries, or policy/advocacy statements," and "[d]ata on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care."[83] FDA refused to consider this information even though it is relevant to whether a REMS is "necessary" for mifepristone; whether the mifepristone ETASU are "commensurate with the specific serious risk[s]" listed in the drug's labeling, and/or "unduly burdensome on patient access to the drug, considering in particular . . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)"; and whether the ETASU "conform with elements to assure safe use for other drugs with similar, serious risks" "so as to minimize the burden on the health care delivery system." *Id.* §§ 355-1(a)(1), (f)(2)(A), (C), (D).

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107. On December 16, 2021, FDA completed its review of the Mifepristone REMS Program and determined that it would: retain the REMS Program; retain the prescriber certification ETASU; retain the patient agreement ETASU; remove the in-person dispensing ETASU; and add a new pharmacy certification ETASU. FDA sent REMS Modification Notification letters to the two drug application holders notifying them that the REMS Program must be retained with these modifications.

[83] *Id.* at 11–12 (emphasis added).

108. In June 2022, the drug application holders submitted supplemental new drug applications consistent with FDA's REMS Modification Notification letters. Over the following months, the application holders held several meetings with FDA, responded to information requests by the Agency, and submitted several amendments to their supplemental applications.

109. On January 3, 2023, FDA completed a subsequent review memorandum ("2023 REMS Review") and released an updated REMS for mifepristone. This constituted a final agency action. It marked the consummation of the Agency's decision-making process and was a decision from which legal consequences flowed.

C. The ~~Mifeprex~~ Mifepristone REMS Confers No Benefit on Patients and Does Not Satisfy the Statutory Requirements for a REMS with ETASU

1. A REMS is Not Necessary to Ensure That the Benefits of ~~Mifeprex~~Mifepristone Outweigh Its Risks

~~91.~~110. The FDCA allows the Agency to impose a REMS 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). None of the six factors the Secretary is statutorily required to consider in making this determination supports ~~the~~ FDA's decision to reauthorize the ~~Mifeprex~~ Mifepristone REMS Program in ~~2016~~2023:

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111. **"The estimated size of the population likely to use the drug involved,"** 21 U.S.C. § 355-1(a)(1): Since Mifeprex's approval in 2000 for use in the United States, medication abortion has, the aAgency noted, "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."[84] Between September 2000 and ~~March 2016~~2022, ~~when the Agency reauthorized the REMS, 2.5~~mifepristone had been used 5.6 million times in the United States. ~~women chose Mifeprex for use to end an early pregnancy~~.

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~~92.~~112. Statutory guidance released by FDA in April 2019 states that, in applying this REMS factor, FDA "considers, among other things, the extent to which that population includes patients expected to use the drug for unapproved uses and the risks associated with those uses."[85] But unlike opioids, which comprised approximately 75% of REMS drugs as of 2019,[86] patients use mifepristone only for its labeled indication—ending a pregnancy—or for other evidence-based reproductive health care like miscarriage care.

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[84] AR 0539.~~2016 Medical Review, *supra* note 1, Ex. A, at 12.~~

[85] U.S. Food & Drug Admin., *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary Guidance for Industry* 9 (Apr. 2019), *available at* https://www.fda.gov/media/100307/download [hereinafter "FDA Statutory Factor Guidance"].

[86] Joint Stip. of Facts ¶ 59.

~~93.~~113. Many more ~~women~~ people could potentially benefit from ~~Mifeprex~~mifepristone. Indeed, the Guttmacher Institute has found that one in four women in the United States will have an abortion during her lifetime, and as SFP observed in its letter to the Agency, "[t]he steady increase in use of medication abortion . . . shows that many women prefer this option, and that it has the ability to improve access to abortion, even in states with restrictive laws."[87]

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~~94.~~114. Because ~~Mifeprex~~ mifepristone has already been safely used by millions of U.S. ~~women~~patients for its approved indication or for another safe, evidence-based regimen endorsed by leading medical authorities like SFP and ACOG,~~,~~ and because increasing access to this medication would help many more, this factor weighs against a REMS.

~~95.~~115. **"The seriousness of the disease or condition that is to be treated with the drug,"** 21 U.S.C. § 355-1(a)(1): The Agency acknowledges that ~~unintended~~ pregnancy is a serious condition. ~~On the same day that it updated the Mifeprex label and reauthorized the REMS (March 29, 2016), the Agency also finally denied a citizen petition filed fourteen years earlier asking the Agency to withdraw the initial (September 2000) approval for Mifeprex. In its~~In a 2016 denial

[87] AR 1254.~~SFP Letter to FDA, *supra* note 29, Ex. H, at 1.~~

of ~~that~~ a citizen petition seeking to withdraw FDA approval for mifepristone, ~~the~~ FDA explained:

> Pregnancy can be a serious medical condition in some women. 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. 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. According to the Institute of Medicine, women experiencing an unintended pregnancy may experience depression, anxiety, or other conditions.[88]

~~96.~~116. Because ~~Mifeprex~~ mifepristone treats a serious condition, and thus offers a substantial potential benefit, this factor weighs against a REMS.

~~97.~~117. **"The expected benefit of the drug with respect to such disease or condition,"** 21 U.S.C. § 355-1(a)(1): In denying the citizen petition asking the

[88] AR 0859. ~~Letter Denying Petition to Revoke Mifeprex Approval, *supra* note 3, Ex. B, at 4-5 (citations omitted).~~

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Agency to withdraw the ~~Mifeprex~~ mifepristone approval, ~~the~~ FDA—on the same day that it reauthorized the REMS—further explained: "[M]edical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion."[89] For instance, in one of the clinical studies conducted in the U.S. shortly before Mifeprex's approval,

> medical termination of pregnancy avoided an invasive surgical procedure and anesthesia in 92 percent of the [study participants]. 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.[90]

~~98.~~118. In addition, some ~~women~~ people prefer medication abortion because it feels more natural, and allows them to pass the pregnancy in the privacy and comfort of their home. Indeed, in its 2016 Medical Review, the Agency noted that "[t]he studies [supporting the Mifeprex labeling changes], *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

[89] AR 0860. ~~*Id.*, Ex. B, at 5 (citations omitted).~~

[90] *Id.* ~~*Id.*, Ex. B.~~

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healthcare system."[91] In short, ~~Mifeprex~~ mifepristone allows ~~a woman~~ patients to have an abortion in a private, comfortable, and safe location, on ~~her~~ their own terms.

119. While misoprostol also has abortifacient properties acting alone, ~~it is safer and more effective in early pregnancy when used in the FDA-approved regimen with~~ the combined regimen of ~~Mifeprex~~mifepristone and misoprostol is the preferred regimen for medication abortion care and the most common regimen for medication abortion care in the United States; and is associated with fewer side effects than the misoprostol-only treatment.

~~7.~~120. Because the benefits that ~~Mifeprex~~ mifepristone offers to patients seeking to end an unwanted pregnancy without surgical intervention are significant and well-established, this factor weighs against a REMS.

~~8.~~121. **"The expected or actual duration of treatment with the drug,"** 21 U.S.C. § 355-1(a)(1): ~~Mifeprex~~ mifepristone is a single 200 mg tablet that is only prescribed for a single use. Korlym, by contrast, is an identical product prescribed for chronic, daily use in dosages ranging from 300 to 1200 mg. Korlym is not subject to a REMS; it is delivered to the patient's home, and the patient is expected to take up to four pills daily per physician instruction. The label includes a boxed warning

[91] AR 0589. ~~2016 Medical Review, *supra* note 1, Ex. A, at 62 (emphasis added).~~

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that Korlym may have abortifacient effects and that patients should not use it if they are pregnant,[92] and the ~~a~~Agency trusts patients to use it accordingly.

~~9.~~122. Because ~~Mifeprex~~ mifepristone is prescribed as a single tablet and poses virtually no risk of misuse, whereas an identical drug that is prescribed in higher doses for daily home administration is not subject to a REMS, this factor weighs against a REMS.

123. **"The seriousness of any known or potential adverse events that may be related to the drug and the background incidence [*i.e.*, frequency] of such events in the population likely to use the drug,"** 21 U.S.C. § 355-1(a)(1): By ~~the~~ FDA's own admission, major adverse events associated with ~~Mifeprex~~ mifepristone are "exceedingly rare, generally far below 0.1% for any individual adverse event."[93] Accordingly, the Agency concluded in March 2016 that it was appropriate to *remove* the requirement that Danco report any hospitalizations, blood transfusions, or other serious events relating to Mifeprex other than death, as the "FDA has received such reports for 15 years, and it has determined that the safety

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[92] AR 0269. ~~Korlym Label, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202107s000lbl.pdf (last visited Sept. 30, 2017).~~

[93] AR 0574. ~~2016 Medical Review, *supra* note 1, Ex. A, at 47.~~

profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely."[94]

124. Similarly, in December 2021, FDA confirmed that "[o]ur review of [mifepristone's] postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced."[95]

125. Mifepristone's FDA-approved labeling explains that "[n]o causal relationship between the use of [mifepristone] and [serious or fatal infections or bleeding] has been established."[96] To the contrary, the FDA-approved Mifepristone Medication Guide acknowledges that the risks listed in the labeling are not inherent to mifepristone, but rather are risks associated with emptying a pregnant uterus by any means: "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

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[94] AR 0535. ~~*Id.*, Ex. A, at 8.~~

[95] Letter from Patrizia Cavazzoni, MD, to Donna J. Harrison, MD & Quentin L. Van Meter, MD, FCP, Re: Docket No. FDA-2019-P-1534 26 [hereinafter "2021 AAPLOG Pet. Denial"], attached hereto as Suppl. Ex. H; *accord* 2021 REMS Review, *supra* note 9, at 22.

[96] AR 384; *accord* AR 387, 398.

abortion, or *childbirth*." (emphasis added).[97] In other words, there is a relatively *high* background incidence of such adverse events among pregnant people generally.[98]

126. Moreover, the Agency acknowledges that "data from the medical literature and findings by the [U.S. Centers for Disease Control and Prevention ("CDC")] suggest that the critical risk factor" in nearly all of the few cases of fatal infections associated with ~~Mifeprex~~ mifepristone "is pregnancy itself," because similar infections "have been identified both in pregnant women who have undergone medical abortion and those who have not[.]"[99]

127. ~~The~~ FDA's 2016 Medical Review also expressly concludeds that "[m]edical abortion in adolescents appears to be at least as safe, if not safer, as in adult women."[100]

~~10.~~128. Because numerous studies and over ~~15 years~~two decades of clinical data in the United States confirm that ~~Mifeprex~~ mifepristone is safe—and that serious adverse events are rare, decreasing, and never shown to have been caused by ~~Mifeprex~~mifepristone—this factor weighs against a REMS.

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[97] AR 383; *accord* AR 0398.

[98] AR 0398 ("[R]arely, serious and potentially life-threatening bleeding, infections, or other problems can occur *following a miscarriage, surgical abortion, medical abortion, or childbirth*." (emphasis added)); *accord* 2021 AAPLOG Pet. Denial, *supra* note 95, at 36.

[99] ~~Letter Denying Petition to Revoke Mifeprex Approval, *supra* note 3, Ex. B, at 26 n.69.~~AR 0880–81 & n.69.

[100] AR 0603. ~~2016 Medical Review, *supra* note 1, Ex. A, at 76.~~

~~11.~~**"Whether the drug is a new molecular entity,"** 21 U.S.C. § 355-1(a)(1): ~~Mifeprex~~ Mifepristone is not a new molecular entity. Mifepristone ~~had already been approved in the United States for nearly 16 years when the FDA reauthorized the REMS in March 2016.~~has been marketed in the United States since 2000, with no new safety concerns since 2005.[101] "Available information about" mifepristone is far from "limited," and there is no "uncertainty about risks associated with the use of the drug that might emerge in the post-approval setting."[102]

~~12.~~129. Because ~~Mifeprex~~ mifepristone is a well-known compound, this factor weighs against a REMS.

130. Finally, because none of these factors supports maintaining the ~~Mifeprex~~ Mifepristone REMS Program, the implementation system and timetable for assessments from the drug manufacturer also are unnecessary. Indeed, as ~~the~~ FDA's 2016 Medical Review acknowledge~~d~~s, even without a REMS, "the [drug manufacturer] 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."[103]

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[101] AR 0354.

[102] FDA Statutory Factor Guidance, *supra* note 85, at 8.

[103] ~~*Id.*, Ex. A, at 8.~~AR 0535.

2. The ~~Mifeprex~~ Mifepristone ETASU Are Not "Commensurate With" and ~~and~~ Do Not Mitigate the "Specific Serious Risk[s]" Listed ~~i~~on the ~~Mifeprex~~ Labeling.

~~99.~~131. In violation of the FDCA, the ~~Mifeprex~~ mifepristone ETASU are not "commensurate with the specific serious risk[s]" listed ~~on Mifeprex's~~in the labeling, 21 U.S.C. § 355-1(f)(2)(A), which are "[s]erious and sometimes fatal infections or bleeding."[104] To the contrary, the ETASU are disproportionate to, have no nexus with, and will not mitigate, the risks listed ~~on~~ in the ~~Mifeprex~~ labeling. ~~In short, there is no relationship between where a woman is standing when she receives the Mifeprex pill and any potential risk of infection or bleeding.~~

~~100.~~132. Moreover, drugs whose risks are similar to or greater than those of ~~Mifeprex~~ mifepristone are not subject to comparable restrictions.

a. The Mifeprex ETASU Are Disproportionate Because Serious Adverse Events Are "Exceedingly Rare"

[104] ~~Mifeprex Label, *supra* note 16, at 1.~~AR 0383.

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133. The Agency concedes that serious adverse events associated with Mifeprex are "exceedingly rare."[105] In its 2016 Medical Review, the Agency concluded: "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 [revised] 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."[106]

~~101.~~134. Similarly, as detailed *supra* ¶ 124, FDA found in 2021 that serious adverse events remained very low even when the in-person dispensing ETASU was eliminated, notwithstanding FDA's insistence from 2000 until April 2021 that this requirement was essential for safe use.

~~102.~~135. In the ~~15~~ nearly 22 years of U.S. post-marketing data available to ~~the~~ FDA when it reauthorized the REMS in 2023, there were only ~~17~~ 28 reported associated deaths out of ~~2.5~~5.6 million uses—an associated fatality rate of 0.000~~568~~%.[107] ~~Since then, there have been only two additional associated deaths~~

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[105] ~~2016 Medical Review, *supra* note 1, Ex. A. at 47.~~AR 0574.

[106] ~~*Id.*, Ex. A, at 84.~~AR 0611.

[107] ~~Id., Ex. A, at 82-83.~~AR 0609-10.

~~out of more than half a million additional uses.~~[108] By contrast, the fatality rate associated with phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction (*e.g.*, Viagra), which are not subject to a REMS, is estimated at 0.0026% of users, roughly ~~4~~ 5 times the ~~Mifeprex~~mifepristone-associated mortality rate.[109]

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~~103.~~136. ~~Five~~ At least 9 of the reported deaths in women who had taken ~~Mifeprex~~ mifepristone involved events clearly unrelated to the medication: ~~, such as~~ narcotic overdose or suspected homicide.[110] And ~~the~~ FDA acknowledges that "[t]here is no information that use of Mifeprex and misoprostol caused" the "very small number" of deaths from infection.[111] Rather, as explained *supra* ¶¶ 125–26, CDC findings and the medical literature suggest that pregnancy itself, not Mifeprex usage, was the "critical risk factor" in nearly all of the (very few) cases of fatal infection.[112]

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~~104.~~137. Indeed, as FDA acknowledges, a woman is at least ~~fourteen~~ 14 times more likely to die if she carries a pregnancy to term than if she uses ~~Mifeprex~~

~~108 Raymond *et al.*, *supra* note 4, at 791.~~

109 Gregory Lowe & Raymond A. Costabile, *10-Year Analysis of Adverse Event Reports to the Food and Drug Administration for Phosphodiesterase Type-5 Inhibitors*, 9 J. Sex. Med. 265, 268-69 (2012).

110 Mifepristone U.S. Post-Marketing Adverse Events, *supra* note 3, at 1.~~,~~

111 ~~Mifeprex Medication Guide 1, *available at* https://www.fda.gov/downloads/Drugs/DrugSafety/UCM088643.pdf (last visited Oct. 1, 2017).~~AR 0261.

112 ~~Letter Denying Petition to Revoke Mifeprex Approval, *supra* note 3, Ex. B, at 26 n.69.~~AR 0880– 81 n.69.

mifepristone to end a pregnancy.[113] Moreover, the two risks listed ion the Mifeprex mifepristone labeling 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 Mifeprex Medication Guide acknowledges: "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*." (emphasis added).[114]

b. The ETASU Do Not "Mitigate" the Risks Listed on in the Mifepristone Labeling

105.138. An essential flaw in the Mifeprex REMS is that there is no nexus between the risks listed on the Mifeprex label and the ETASU—they do not serve to "mitigate" any such risks, as required by 21 U.S.C. § 355-1(f)(1)(A). Specifically:

i. ETASU D: Patient Agreement

106.139. Every one of the FDA experts who participated in the Agency's formal March 2016 review for Mifeprex concluded that the Patient Agreement form

[113] AR 0859 & n.6 (citing 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)).

[114] Mifeprex Medication Guide 1, *supra* note 69, at 1.

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provides no medical benefit.

~~107.~~140. Those unanimous conclusions were amended only after ~~then FDA~~defendant Commissioner Robert Califf requested that this ETASU be maintained nonetheless. The sole rationale for the Commissioner's unusual intervention is documented in a memorandum from Director Woodcock, in which she states that "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."[115]

141. Commissioner Califf made this request notwithstanding that medication abortion does not involve any "procedure," only pills, and notwithstanding that ~~the~~ FDA's 2016 Summary Review "concur[red] with the clinical review team that the Patient Agreement Form, which requires a patient's signature," is duplicative of existing informed consent laws and standards, "does not add to safe use conditions for the patient for this REMS[,] and is a burden for patients."[116]

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[115] AR 0674. ~~Woodcock Patient Agreement Memo, *supra* note 10, Ex. D, at 1.~~

[116] AR 0437, 0674. ~~2016 Summary Review, *supra* note 9, Ex. C, at 25.~~

142. In its 2021 review, FDA "agree[d] that informed consent in medicine is an established practice" as a general matter,[117] and specifically found that a survey of abortion providers in the United States and Canada in 2017 "did reveal strong adherence to evidence-based guidelines."[118]

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143. Nevertheless, FDA noted that "removal of the in-person dispensing requirement could significantly increase the number of [mifepristone] providers to a larger group of practitioners,"[119] and reasoned that the Patient Agreement ETASU will ensure that "each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care."[120]

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144. FDA offered no explanation at all for why a special counseling form is necessary to ensure adequate counseling by new prescribers with respect to the use, risks, and follow-up care for mifepristone—a medication with a well-established risk profile, which has been available in the United States for nearly a quarter of a century—when FDA approves *entirely new drugs* all the time without a patient agreement form, even though *every* prescriber will be unfamiliar with that novel medication.

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[117] 2021 REMS Review, *supra* note 9, at 17.

[118] *Id.*

[119] *Id.*, at 18; *accord id.* at 37; 2023 REMS Review, *supra* note 8, at 11–12.

[120] ~~*Id.*~~ 2021 REMS Review, *supra* note 9, at 18.

145. Moreover, mifepristone already has a special "medication guide" as part of its labeling that discusses mifepristone's use, risks, and follow-up care. The 2016 FDA review team specifically found the patient agreement form "duplicative" of the mifepristone medication guide, which "contains the same risk information covered under the Patient Agreement form,"[121] using patient-friendly language.[122] Yet FDA nowhere addressed this duplication in its 2021 or 2023 reviews.

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~~ii. ETASU C: Restricted Distribution~~

~~108. ETASU C provides that Mifeprex may be dispensed only in certain health care facilities and not in retail pharmacies. Although in 2016 the FDA "assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks[,]"[123] the Agency's only documented rationale for this ETASU is that it "ensures that Mifeprex can only be dispensed by or under the direct supervision of a certified prescriber."[124]~~

~~109. This explanation is medically unjustified for several reasons.~~

~~110. *First*, although ETASU C requires that Mifeprex be *dispensed* only in a clinic, medical office, or hospital, it does not require that the patient *take* the~~

[121] Joint Stip. ¶ 57.

[122] *Id.* ¶ 41.

~~[123] 2016 Supplement Approval Letter, *supra* note 40, Ex. I, at 2.~~

~~[124] 2016 REMS Modification Memorandum, *supra* note 19, Ex. E, at 3.~~

~~Mifeprex only in a clinic, medical office, or hospital. A provider may give her the Mifeprex to take at home, just as they may give her the misoprostol to take at home, or give her a prescription to obtain the misoprostol at a pharmacy and then take at home. Where a woman takes the Mifeprex is a function of the exigencies of her life: she knows when and where she wants to be when she passes the pregnancy; from that decision, she works backward to decide when and where to take first the Mifeprex and then the misoprostol.~~

~~111. The FDA's 2016 Medical Review notes that "[t]he 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."[125] The memorandum describes another study as including "safety" among the benefits of home administration of Mifeprex and misoprostol.[126]~~

~~112. There is *no* safety benefit to requiring that a woman be handed a single pill at a clinic, medical office, or hospital to be swallowed at home, rather than be handed a single pill at a retail pharmacy to be swallowed at home.~~

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~~[125] 2016 Medical Review, *supra* note 1, Ex. A, at 62.~~

~~[126] *Id.*, Ex. A.~~

~~113. *Second*, the pharmacologic effects of Mifeprex do not begin until hours after ingestion, and as the label explains, "most women will expel the pregnancy within 2 to 24 hours of taking *misoprostol*"[127] i.e., 26 to 72 hours after taking the Mifeprex. Thus, regardless of where the woman takes the Mifeprex or misoprostol, she will almost never be under the direct supervision of her prescriber by the time the bleeding (a necessary part of the miscarriage) begins.~~

~~114. In short, banning pharmacists from dispensing Mifeprex once it has been prescribed to a patient has no bearing on whether, hours later, a woman will have the "exceedingly rare" experience of one of the risks listed on the label.~~

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ii~~i~~. ETASU A: Special Certification for Prescribers

~~115.~~146. To become certified to prescribe ~~Mifeprex~~mifepristone, health care providers must submit a form attesting that they (1) can assess the duration of pregnancy accurately; (2) can diagnose ectopic pregnancies; (3) can provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and (4) have read and understood the prescribing information.

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~~[127] Mifeprex Label, *supra* note 16, at 3.~~

147. In 2016, ~~T~~the Agency's only documented rationale for maintaining ETASU A wa~~i~~s that it "ensures that Mifeprex can only be dispensed by or under the direct supervision of a certified prescriber"[128]—a pure tautology. ~~(the same as ETASU C).~~

148. In 2023, FDA reauthorized this ETASU because its "review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol."[129]

~~116.~~149. But FDA's rationale is premised on two wholly unsupported, purely speculative premises: (1) that clinicians providing pregnancy-related care would not already possess these fundamental abilities; and/or (2) that, in the absence of this ETASU, clinicians would prescribe mifepristone despite lacking appropriate qualifications.

~~117.~~150. ~~This~~ FDA's explanation is medically unjustified for several reasons.

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[128] ~~2016 REMS Modification Memorandum, *supra* note 19, Ex. E, at 3.~~AR 0681.

[129] 2023 REMS Review, *supra* note 8, at 13–14; *accord, e.g.*, *id.* at 36; *accord* 2021 AAPLOG Pet. Denial-, *supra* note 95, at 23.

~~118.~~151. *First*, numerous other mechanisms, including licensing requirements, ethical and professional obligations, and malpractice liability, exist to ensure that health care providers practice only to the extent of their training and abilities. An attestation of competency provides no greater assurance that a health care provider will not provide care outside of their scope of practice than do these existing legal requirements and ethical norms.

~~119.~~152. *Second*, there are countless other drugs that require careful patient screening to ensure safe use, yet are not subject to ETASU. Indeed, clinicians are not required to make a comparable attestation of their qualifications before prescribing Korlym—which is the *exact same product* as Mifeprex (mifepristone), in higher doses.

~~120.~~153. *Third*, fulfilling these criteria requires no specialized medical expertise. ~~Any~~ FDA has conceded that any provider who is not comfortable using patient medical history or a clinical examination to assess the duration and location of a pregnancy can obtain that information by ordering an ultrasound.

154. Similarly, any provider can arrange for emergency care by referring patients to an emergency room in the rare event that such care is needed. Indeed, as FDA acknowledged in a citizen petition denial issued on the *very same day* the Agency completed its December 2021 REMS Review concluding that the Prescriber

ETASU must be retained: "It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients."[130]

~~13.~~155. *Fourth*, as discussed *infra*, due to a number of factors, including the REMS, many patients ~~forces some patients to~~are forced to travel outside their communities for abortion care. A patient who receives ~~Mifeprex~~ mifepristone from a REMS-certified provider outside her community and then initiates her medication abortion once she is back home generally will not (and should not) travel to seek in-person follow-up care from her REMS-certified prescriber; instead, she will receive any such follow-up care in her own community. The certification of the ~~Mifeprex~~ mifepristone prescriber thus has no bearing on the care the patient would receive in the unusual event of a complication.

156. *Finally*, reading and understanding the prescribing information for ~~Mifeprex~~ mifepristone is well within the scope of practice for any licensed prescriber.

iii. ETASU B: Pharmacy Certification

157. In order to dispense mifepristone, a pharmacy must become REMS-certified, which means agreeing to take on significant costs and burdens far beyond what is required for virtually every other prescription drug. These requirements

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[130] 2021 AAPLOG Pet. Denial, *supra* note 95, at 12.

include (but are not limited to) verifying that mifepristone prescriptions are written only by REMS-certified prescribers and storing prescriber certification information in a manner that is both dynamic and confidential; tracking shipments of mifepristone by mail; engaging in two-way communications with the mifepristone prescriber regarding the timing of the medication's delivery; "reporting any patient deaths" (with no further clarification as to what this reporting entails); and being regularly audited for REMS compliance.

158. FDA concedes that the Pharmacy Certification ETASU is burdensome and will deter pharmacies from dispensing mifepristone: the Agency "acknowledge[d] that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS."[131] And FDA did not even account for any of the other burdens imposed by this ETASU beyond verifying prescriber certification, and their inevitable deterrence effect on pharmacy participation.

159. FDA justified adding this new ETASU based principally on its interaction with the prescriber certification requirement. FDA explained that "[w]ithout pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber."[132] The purpose of this ETASU is to

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[131] 2023 REMS Review, *supra* note 8, at 14.

[132] *Id.*, ~~*supra* note 8,~~ at 13.

"incorporate[] pharmacies into the REMS, ensure[] that pharmacies are aware of and agree to follow applicable REMS requirements, and ensure[] that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers."[133]

~~121.~~160. FDA nowhere addressed the fact that pharmacies had already been dispensing mifepristone for more than a year—from July 2020 until January 2021, and from April 2021 until December 2021—with *no* certification requirement and no increase in adverse events. Indeed, by January 3, 2023—when FDA completed its 2023 REMS Review, reauthorized the REMS, and for the first time imposed the Pharmacy Certification ETASU—pharmacies had been safely dispensing mifepristone without certification for well over two years.

c. Drugs That Pose Similar or Greater Risks Than ~~Mifeprex~~ Mifepristone Are Not Subject to Comparable Restrictions

~~122.~~161. The FDCA requires that, "to the extent practicable," ETASU "conform with elements to assure safe use for other drugs with similar, serious risks[.]" 21 U.S.C. § 355-1(f)(2)(D). But most other drugs that pose similar or greater risks than ~~Mifeprex~~ mifepristone are not subject to comparable restrictions.

[133] *Id.*

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~~123. Today, according to the FDA's REMS database, only 73 of the nearly 1800 prescription drugs and therapeutic biologic active ingredients approved by the FDA and marketed in the United States are subject to a REMS.[134]~~

~~124. Only 43 of those, including Mifeprex, are subject to a REMS *with* ETASU.[135] Thus, in effect, the Agency has classified Mifeprex alongside drugs such as OxyContin® and other opioids as one of the 43 drugs with the most "inherent toxicity or potential harmfulness" available in the United States. And even within the group of 43 drugs that are subject to a REMS with ETASU, only a handful, including Mifeprex, are subject to the stringent restriction that the drug be dispensed only in certain health care settings and not in a pharmacy by prescription.~~

162. As of November 2019, fewer than 3% of FDA-approved prescription drug products were subject to a REMS, 75% of which were opioids.

~~125.~~163. ~~Moreover, m~~Many drugs that have higher safety risks than ~~Mifeprex~~ mifepristone are permitted to be marketed without restrictions comparable to the Mifeprex REMS.

~~126.~~164. For instance, Viagra is associated with death in up to 0.0026% of users, roughly ~~4~~ 5 times the ~~Mifeprex~~mifepristone-associated mortality rate.[136] And

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~~[134] FDA REMS Count, *supra* note 5; Raymond *et al.*, *supra* note 4, at 791.~~

~~[135] FDA REMS Count, *supra* note 5.~~

[136] Lowe & Costabile, *supra* note 109, at 268-69.

acetaminophen (Tylenol) toxicity is the most common cause of liver transplantation in the United States, and responsible for 56,000 emergency department visits, 2,600 hospitalizations, and 500 deaths per year in this country. Yet, neither ~~according to the FDA's REMS database,~~ Viagra ~~does~~ nor Tylenol has~~not have~~ a REMS.[137]

165. Similarly, as the *Chelius* Plaintiffs highlighted in their letter to FDA—and FDA nowhere addressed—many anticoagulant products, commonly known as "blood thinners," are associated with "serious and fatal bleeding," and, like ~~Mifeprex~~mifepristone, carry warnings of that risk on their FDA-approved labels.[138] But unlike ~~Mifeprex~~mifepristone, anticoagulants are a frequent cause of emergency room visits for documented hemorrhage.[139] Yet anticoagulants are available by prescription ~~at a pharmacy~~without a REMS, whereas Mifeprex is not.

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[137] Suneil Agrawal & Babak Khazaeni, Acetaminophen Toxicity, Nat'l Library of Med. (Aug. 1, 2022), *available at* https://www.ncbi.nlm.nih.gov/books/NBK441917/#:~:text=It%20is%20responsible%20for%2056%2C000,is%20contained%20in%20combined%20products.

[138] *See, e.g.*, Coumadin® label, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf (containing boxed warning for, *inter alia*, "major or fatal bleeding"); Pradaxa® label, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022512s027lbl.pdf (warning of "serious and fatal bleeding"); Xarelto® label, *available at* https://www.xareltohcp.com/shared/product/xarelto/prescribing-information.pdf (same).

[139] Nadine Shehab, *et. al.*, *US Emergency Department Visits for Outpatient Adverse Drug Events*, 2013-2014, 316 J. Am. Med. Ass'n 2115-25 (2016) (17.6% of emergency room visits based on adverse drug events in 2013-2014 were related to anticoagulants, and of those, roughly 80% involved documented hemorrhage).

~~127.~~166. The *Chelius* Plaintiffs also highlighted in their letter to FDA that Jeuveau® is indicated for a purely cosmetic purpose among a healthy population—the "temporary improvement in the appearance of moderate to severe glabellar lines" (i.e., lines between one's eyebrows). It carries a black-box warning for "[s]wallowing and breathing difficulties" that "can be life threatening" if this botulinum toxin product spreads beyond the area of injection, and the labeling notes "there have been reports of death."[140] Yet FDA nowhere explained in its 2021 or 2023 REMS reviews why a REMS is necessary for mifepristone but not for Jeuveau.

~~128. Perhaps most telling is that, despite the prescription opioid abuse crisis—which is estimated to result in more than 22,000 overdose deaths in the United States each year (about 62 people per day)[141]—opioid products are permitted to be dispensed at pharmacies. But Mifeprex is not.~~

~~129.~~167. In sum, the ~~Mifeprex~~ Mifepristone REMS ~~with~~ and its ETASU ~~is a~~are medically unjustified restrictions on abortion, as evidenced both by the drug's own record and by how ~~the~~ FDA regulates other drugs with a safety profile comparable to or weaker than that of ~~Mifeprex~~mifepristone.

~~130.~~168. These restrictions simply are not motivated by science.

[140] Jeuveau Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761085s000lbl.pdf (Feb. 2019).

~~[141] U.S. Ctrs. for Disease Control & Prevention, Opioid Data Analysis (Feb. 9, 2017), *available at* https://www.cdc.gov/drugoverdose/data/analysis.html.~~

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D. The Impact of the ~~Mifeprex~~ Mifepristone REMS on Plaintiffs, Plaintiffs' Members, and Plaintiffs' Members' Patients

1. Harms Caused by the 2023 REMS

169. FDA's 2023 REMS reauthorization extends many of the same kinds of burdens on patients and the health care delivery system that FDA's unique restrictions on mifepristone have imposed from the beginning.

170. ***First***, by continuing to classify mifepristone as among the tiny fraction of drugs for which REMS restrictions are necessary—on par with dangerous opioids causing "staggering" numbers of deaths each year—FDA's REMS reauthorization sends a false message about mifepristone's safety that complicates, delays, and derails efforts by health care providers to prescribe, research, and/or provide trainings on mifepristone.

171. For instance, clinicians seeking to begin prescribing mifepristone at their hospital or clinic have been required by health system leadership and/or decision-making committees to put together special presentations on mifepristone safety that are not required for other drugs with safety records comparable to mifepristone before the health care provider is permitted to prescribe it and/or the health system pharmacy is permitted to stock it. Such bureaucratic hurdles delay—and in some cases entirely prevent—health care providers in providing mifepristone to their patients, and would not arise if mifepristone were not subject to a REMS.

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172. As another example, clinicians in doctoral programs have been unable to complete research and training projects relating to mifepristone because of institutional concerns and stigma expressly relating to mifepristone's classification as a REMS drug—e.g., requiring a doctoral student to seek Institutional Review Board ("IRB") approval for a project that would not otherwise necessitate IRB approval, because it involves "a REMS drug."

173. ***Second***, FDA's REMS reauthorization still means that a clinician seeking to prescribe mifepristone often must involve many other colleagues in their health system—such as administrators, nurses, and information technology staff—in the provision of mifepristone, which can delay or altogether derail their ability to provide this medication to their patients.

174. For instance, because FDA requires mifepristone prescribers to be specially certified, health systems may need to develop special systems to track and update clinicians' certifications. Because FDA requires mifepristone patients to sign a special counseling form, health care facilities that use electronic medical records must come up with a system for storing the signed Patient Agreement form in the patient's medical record, and health care facilities that wish to utilize telemedicine for mifepristone must implement HIPAA-compliant technology to allow for patients to remotely sign the Patient Agreement.

175. These and other logistical and technological burdens imposed by the REMS—layered on top of the broader deterrent effect of the REMS classification—frequently prevent patients from obtaining a mifepristone prescription from their primary health care provider.

176. ***Third***, by maintaining the Prescriber Certification ETASU, FDA continues to substantially reduce the pool of qualified health care providers willing to prescribe mifepristone because many clinicians are fearful that they will face anti-abortion violence and harassment if their registration as a mifepristone prescriber were ever exposed. FDA's own actions underscore the severity of this concern: the Agency redacted from the administrative record in this matter the names and offices of every one of its employees who has done any work relating to mifepristone. FDA explained that it feared that, "[i]n light of the violence and harassment surrounding the provision of abortion," releasing this information—*even subject to a protective order designed to ensure the confidentiality of that information*—"could expose those employees to threats, intimidation, harassment and/or violence."[142]

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177. These fears are heightened now due to the growing criminalization and penalization of abortion care in many states across the country following *Dobbs v. Jackson Women's Health Org.*, with a particularly chilling effect on clinicians who

[142] Joint Stip. of Facts. ¶ 47.

hold medical licenses in multiple states, or medical residents who intend to eventually practice in a state with severe abortion restrictions. For instance, in recent years, several states have enacted laws allowing "bounty-hunter" vigilantes to drag into court anyone whom they suspect to have aided in the performance of an unlawful abortion, with no opportunity for the person sued to recover their litigation costs and fees even if they ultimately prevail. *See, e.g.*, Tex. Health & Safety Code § 171.208; Idaho Code Ann. § 18-8807.

178. ***Fourth***, by maintaining the Patient Agreement ETASU, FDA also retained a *de facto* in-person pill pick-up requirement for patients seeking mifepristone who do not themselves have the technology for a remote signature—e.g., no access to a smartphone or computer—or who seek mifepristone at a health center that does not have the technology in place to enable HIPAA-compliant remote signatures. As detailed *infra*, this is one of the many ways in which the 2023 REMS disproportionately harms low-income communities and communities of color.

179. ***Fifth***, the Patient Agreement ETASU *undermines* informed consent by requiring patients to review and sign a form containing fossilized science that may be inconsistent with their individual clinical circumstances. For example, the Patient Agreement states that the patient will take the misoprostol "24 to 48 hours" after taking the mifepristone. But some clinicians instruct patients to use an evidence-based protocol in which the misoprostol is taken simultaneously with mifepristone,

or at another timeframe shorter than 24 hours, consistent with high-quality research and the patients' individual circumstances.[143] At best, the Patient Agreement duplicates counseling that mifepristone prescribers would already do, consistent with professional and ethical standards. More often, it complicates and confuses the counseling—particularly for patients with limited English proficiency who need translation services.

180. The Patient Agreement is often particularly confusing and distressing for patients using mifepristone for miscarriage care, who must attest that they are taking the medication "to end [their] pregnancy," even when this is false. Clinicians unwilling to require their patients undergoing miscarriages to sign a form containing knowingly false information about their medical condition and decision—or who work at a health care facility whose administration is concerned about the confusion or liability resulting from such a requirement—are unable to prescribe mifepristone to their patients experiencing early pregnancy loss at all.

181. ***Sixth***, by compelling patients using mifepristone to sign and take with them a form stating that they have had an abortion, FDA's REMS Reauthorization jeopardizes patients' privacy—because of the risk that the form will inadvertently be found by others with whom the patient might not otherwise disclose their

[143] *See, e.g.*, Nat'l Abortion Fed., 2022 Clinical Practice Guidelines 19 (2022), *available at* https://prochoice.org/wp-content/uploads/2022-CPGs.pdf.

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pregnancy and/or abortion decision. Relatedly, by requiring that patients sign and take with them a form in which they attest that they have had an abortion, this ETASU increases the risk that patients will face anti-abortion violence and harassment (even if they actually used the mifepristone for miscarriage treatment).

182. ***Seventh***, the Pharmacy Certification ETASU imposes significant costs and burdens that deter pharmacies—especially smaller community pharmacies—from dispensing mifepristone, reducing patients' access to this medication. In order to comply with this ETASU, pharmacies seeking to dispense mifepristone must have the infrastructure and human and financial resources to, *inter alia*, develop a system to confidentially maintain prescriber certifications; verify that any prescription sent in for mifepristone comes from a certified prescriber; if the prescription does not come from a certified prescriber, either contact the prescriber to try to verify their certification or inform the patient that the prescription cannot be filled (in either case, delaying the patient's access); and train staff and prepare for special audits of their mifepristone REMS compliance procedures.

183. The Pharmacy Certification ETASU also necessitates that pharmacies commit to fill mifepristone prescriptions by mail using a carrier service that will ensure the medication is delivered within four calendar days, and if it appears the shipment may take more than four calendar days to arrive—e.g., due to a shipment delay or incomplete patient address—attempt to contact the prescriber to confirm

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"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 then maintain records documenting the prescriber's decision. By requiring that all shipments arrive within four calendar days except with documented confirmation from the prescriber, the Pharmacy Certification ETASU necessitates that pharmacies use more expensive carrier services—and then either absorb those costs themselves (a further deterrent to become certified) or else pass those costs on to patients. This ETASU strips patients of the autonomy to choose a less expensive shipping option even if they know that, given the length of their pregnancy, receiving the medication in slightly more than 4 days would still be perfectly fine.

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184. While some larger pharmacy chains or national mail-order pharmacies may be able to bear the financial and logistical burdens of the REMS requirements, mail-order delivery is not an appropriate option for many patients, such as those who are homeless or housing insecure or those living with an abusive partner or parent from whom they must keep their abortion decision private.

185. ***Eighth***, by prohibiting all but certified pharmacies to dispense mifepristone, FDA's REMS Reauthorization makes it practically impossible for many health care providers to know where to send the patient's prescription for fulfillment, particularly if the patient does not live in the prescriber's immediate area. There is no system to enable prescribers to know which pharmacies are certified.

Without a REMS, clinicians can generally send in a prescription to the patient's preferred pharmacy, which will fill the medication if they have it in stock; request the medication from their pharmaceutical vendor; or else transfer the prescription to another pharmacy able to fill it. But the Pharmacy Certification ETASU replaces this common and common-sense process with confusion and delay, and will necessitate that busy health care providers call around to multiple pharmacies or try to do research online in order to determine where to send the patient's prescription.

186. For the reasons described *supra* ~~¶¶ 19-20, 78-79, 103-106, 169-185~~ and others, the 2023 Mifepristone REMS Program unduly burdens patients' access to a safe and effective medication, compounding the profound abortion access issues that already exist in the United States—including in states where abortion remains legal after *Dobbs*. The REMS thus specifically harms "patients who [already] have difficulty accessing health care." 21 U.S.C. §355-1(f)(2)(C)(ii).

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187. As the *Chelius* Plaintiffs highlighted in their 2021 submission to FDA, and FDA expressly ignored (*see supra* ¶¶ 103–06):

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> A nationally representative sample of 8,000 abortion patients found that patients traveled, on average, 68 miles round-trip to receive an abortion. In a majority of states, at least 20% of reproductive-age women live more than 100 miles round-trip from the nearest abortion clinic. And while rural areas are particularly lacking, patients in urban areas also struggle. A 2018 study found that 27 major

> cities have no publicly advertised abortion provider within 100 miles.[144]

188. Like all restrictions on abortion, the burdens of the Mifepristone REMS Program are not borne equally. As the *Chelius* Plaintiffs explained, restrictions that necessitate that patients travel farther in order to find a mifepristone provider, or make an extra medically unnecessary trip to a health center just to sign a form, can make it "incredibly difficult and in some cases impossible" for patients with unwanted pregnancies to access any abortion care at all.[145]

189. The REMS burdens are particularly harmful "[g]iven the mifepristone patient population."[146] As Plaintiffs explained:

> [I]n 2014 (the most recent year for which such data are available), 75 percent of abortion patients had incomes at or below the U.S. Official Poverty Measure. Sixty percent of abortion patients identify as people of color, including 53 percent of patients who identify as Black or Hispanic. And 60 percent of abortion patients have at least one child.[147]

By further reducing where abortion care is available in this country, the *Chelius* Plaintiffs told FDA, the REMS "imposes costs and burdens relating to transportation, childcare, and lost wages for missed work that many in this patient

[144] Chelius Plaintiffs' Letter, *supra* note 10, at 5; *accord id.* at App. 089-122.

[145] *Id.*

[146] *Id.* at 5.

[147] *Id.* at 5–6.

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population simply cannot afford. Indeed, a robust body of research, spanning multiple states and decades, confirms that forcing patients to travel even slightly farther (e.g., 10 miles) delays or blocks patients from accessing desired abortions."[148]

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190. In addition to reducing the number of mifepristone prescribers, the 2023 REMS poses specific burdens for, *inter alia*, low-income populations (in which people of color are disproportionately represented because of structural racism), homeless populations (which disproportionately include LGBT people), people with limited English proficiency, and people living in abusive households. For example, without reliable and private access to a smartphone or computer with which to remotely sign the Patient Agreement form, patients are forced to make a wholly unnecessary trip to the health center when they could otherwise obtain their medication by mail or (potentially) at a local pharmacy. Likewise, people with housing insecurity who do not have a reliable mailing address must find and travel to a health center that stocks and dispenses mifepristone onsite when the burdens of the Pharmacy Certification ETASU prevent local retail pharmacies from stocking mifepristone. FDA failed to consider these and many other ways in which the mifepristone ETASU disproportionately harm patients that already face difficulties accessing healthcare.

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[148] *Id.* at 6.

2. Illustrative Harms to Plaintiffs and Plaintiffs' Members

191. Dr. Chelius is now able to prescribe mifepristone through a mail-order pharmacy, but he and his patients continue to experience harm as a result of the REMS. In particular, the REMS jeopardizes the privacy of Dr. Chelius's patients who need medication abortion care. Kauai Veterans, where Dr. Chelius works, is located in Waimea, a small town of fewer than 2,000 people on the western side of Kaua'i. Kauai Veterans employs nearly 500 people across the island, with the majority working at its Waimea hospital and clinic site; many employees, including Dr. Chelius, live nearby in the Waimea area. Most members of the community have a family member, friend, or neighbor employed at the hospital. Dr. Chelius recently provided a medication abortion to a patient who is a member of hospital staff. Generally, patient records are maintained through an electronic medical system, but the system does not have the capacity to store the Patient Agreement form—a unique form generated outside of the hospital system (*i.e.*, by FDA) that would need to be scanned in from a hard copy. In order to comply with the requirement in the Prescriber Agreement form that prescribers "ensure that the signed Patient Agreement Form is placed in the patient's medical record," Dr. Chelius would have to involve administrative staff in creating a hard copy file for his patient, thus revealing her private medical decision to her colleagues. In addition to causing direct harm to this patient and jeopardizing Dr. Chelius's relationship with someone who

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is both a patient and a colleague, Dr. Chelius is concerned about potential HIPAA implications of the Patient Agreement ETASU. In the insular community in which Dr. Chelius lives and works, there is a strong likelihood that similar privacy issues will arise again as a result of the REMS.

192. At this time, there are no brick-and-mortar pharmacies on Kaua‘i that are dispensing mifepristone. Several pharmacies on the island have indicated publicly or to Dr. Chelius or his colleagues that they would be willing to dispense mifepristone, but are uncertain whether they will be able to fulfill the requirements of the Pharmacy Certification ETASU and are still navigating those barriers. As previously detailed in this litigation, Dr. Chelius is unable to procure, stock, dispense, and bill for mifepristone onsite at his hospital because of opposition to abortion by colleagues who would need to be involved in those tasks, and because of the confidentiality concerns that doing so would pose in his tight-knit community. Establishing retail pharmacy access for mifepristone on the island is therefore critical for many of Dr. Chelius’s patients for whom mail-order delivery is a poor option, for instance because they are homeless. Local access is particularly urgent for Dr. Chelius’s patients who are nearing the gestational age limit for mifepristone because of both the logistics and cost of expedited delivery to the island of Kaua‘i—with overnight delivery from the contiguous United States being virtually impossible, and exacerbated by the time difference.

193. SFP and CAFP each has members experiencing harm(s) traceable to the REMS, including many or all of the harms detailed *supra*. For instance:

194. Sarah McNeil, MD, is a member of both SFP and CAFP and a family medicine doctor. Among other work, Dr. McNeil provides primary care, including mifepristone for abortion and miscarriage, within a large county health system in northern California primarily serving a low-income patient population disproportionately comprising people of color. While there are more than 20 primary care offices located throughout the county—often hours apart from each other by car or bus—mifepristone is typically only prescribed at a single site within the county health system, and the REMS is impeding Dr. McNeil and her colleagues from expanding the provision of mifepristone to outlying clinics. She and her colleagues have already spent tens of hours over multiple years trying to navigate the administrative barriers imposed by the REMS, and developing technology to increase awareness of the REMS among clinicians across the health system and streamline their ability to make mifepristone available for abortion and miscarriage care. These efforts have yielded only limited success, and Dr. McNeil's work to surmount the REMS barriers is ongoing.

195. For instance, as a direct result of the Prescriber Certification ETASU, Dr. McNeil's health system requires that would-be mifepristone prescribers go through the added hurdle of obtaining internal privileges for mifepristone through

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their Medical Staff Office. To become credentialed, a clinician must submit an application that is then reviewed by the credentialing committee through a formal process occurring only once per month—delaying a clinician's ability to integrate mifepristone into their practice. Dr. McNeil's health system does not require OB-GYN or Family Medicine doctors to obtain privileging before prescribing *any* other medication—only mifepristone.

196. As another example, the REMS creates an array of challenges for Dr. McNeil and her colleagues with respect to mifepristone dispensing. After countless meetings and emails with the numerous colleagues that must be involved in REMS compliance, Dr. McNeil's health system recently developed a process for its inpatient pharmacy to maintain records of whether a clinician is certified to prescribe mifepristone, and to dynamically update the system's electronic health records to reflect that information—a substantial and ongoing investment of human labor.

197. Even with this system in place, the Prescriber Certification ETASU is likely to still cause confusion and delays in patient care. Dr. McNeil's system has determined that, if a clinician unaware of the REMS requirements submits a mifepristone prescription to the health system's inpatient pharmacy without already being REMS-certified, someone at the inpatient pharmacy—which is also responsible for, *e.g.*, filling time-sensitive prescriptions for the hospital's intensive care unit—will have to send a copy of the certification form to that prescriber, who

must then print, sign, and fax it back to the inpatient pharmacy before the prescriber can be considered temporarily privileged for mifepristone and the medication can be dispensed. Alternatively, if a clinician working at one of the few clinics in the county health system that stock mifepristone onsite writes a prescription for a patient without having already been REMS-certified, the nurse responsible for dispensing medications would have to notify the prescriber that certification is required before it can be dispensed; the clinician would then have to coordinate with the inpatient pharmacy to complete their certification and fax it to the pharmacy; and the pharmacy would then have to get in touch with the nurse to give the green-light to dispense the mifepristone. Meanwhile, the patient either must wait at the clinic for this entire process to be completed in order to obtain their prescription, or else leave the clinic—for instance, because of work or family responsibilities—and then make another trip back at a later time to obtain the pill, with all of the burdens and costs of transportation, child care, and time off work that entails.

198. Dr. McNeil shares her story in her individual capacity and as an SFP and CAFP member, and not as a representative of any other institution.

199. Julie Jenkins, DNP, APRN, WHNP-BC, is a member of SFP and a nurse practitioner specializing in women's health who also holds a Doctor of Nursing Practice degree. The Doctor of Nursing Practice degree culminates in a final project intended to provide the doctoral candidate with an opportunity to publish and

to gain other meaningful experience that will help position them for the academic job market. Dr. Jenkins intended to focus her project on developing and implementing a training on mifepristone for advanced practice registered nurses, the methodology and results of which she would then publish. However, Dr. Jenkins faced repeated REMS-related hurdles in attempting to implement this straightforward project. For instance, while IRB approval would normally not be required for a project of this nature, Dr. Jenkins was advised by leadership at her academic institution to seek IRB approval—expressly because of mifepristone's REMS classification. Despite months of efforts to try to overcome these barriers, Dr. Jenkins was unable to complete the project at all, forfeiting an important professional opportunity. Indeed, Dr. Jenkins later had to explain in a job interview for an academic position why she did not complete a project during her doctoral program, and ultimately did not get that job.

200. Dr. Jenkins shares her story in her individual capacity and as an SFP member, and not as a representative of any other institution.

201. Angela Chen, MD, is a member of SFP and an OB-GYN practicing in a large university medical center in Los Angeles. Dr. Chen is a certified prescriber in the mifepristone REMS Program who prescribes mifepristone to patients seeking medication abortion and miscarriage care. But the Prescriber Certification ETASU poses significant burdens for Dr. Chen and her colleagues. Dr. Chen has colleagues

within her institution and at the institution's satellite clinics who, although trained to provide medication abortion and miscarriage care with mifepristone, do not prescribe mifepristone because of the Prescriber Certification ETASU. These colleagues have informed Dr. Chen that they are not comfortable becoming certified prescribers because of concerns about security and stigma if they were ever publicly identified as an abortion provider. Instead, they refer their patients who need mifepristone for medication abortion or miscarriage care to Dr. Chen and other certified prescribers in her practice. Similarly, OB-GYNs, family medicine physicians, internal medicine doctors, pediatricians, and other clinicians who practice in private settings and in community health centers in the Los Angeles area regularly refer patients to Dr. Chen and her colleagues for medication abortion and miscarriage care using mifepristone because they are unwilling or unable to become REMS-certified. These referrals occur nearly every week. Because of the frequency with which the referrals occur, and the time-sensitive medical care involved, these referrals impose burdens and logistical challenges for the certified prescribers as well as other institutional staff who have to work to try to squeeze these patients into already packed schedules.

202. The Patient Agreement ETASU also burdens Dr. Chen and her patients. Dr. Chen's institution uses an electronic medical record and e-signature system that could not accommodate the Patient Agreement form required under the REMS. As

a result, they had to set up an entirely new system, separate from their existing system, to obtain e-signatures from the patients prescribed mifepristone. But even this does not fully solve the problem, because Dr. Chen and her colleagues have some patients who do not have smart phones or computers with which to sign the form remotely. As a result, those patients must make an entirely unnecessary in-person trip to the health center just to sign the Patient Agreement form and pick up the pill, with all of the costs and logistics—including transportation, child care, and time off work—such travel entails. If not for the REMS, those patients could obtain their medication by mail (or at a local pharmacy) without having to make a trip to Dr. Chen's office.

203. The Patient Agreement ETASU has also imposed emotional harm on some of Dr. Chen's patients seeking care for miscarriage, because they are forced to sign a form that says they have decided to take mifepristone to end their pregnancy when they are, in reality, suffering the loss of a wanted pregnancy.

204. Dr. Chen shares her story in her individual capacity and as an SFP member, and not as a representative of any other institution.

205. Zeynep Uzumcu, MD, is a member of CAFP and a family medicine doctor specializing in obstetrics care. Among other work, she provides primary care at a safety net community health center serving a low-income population, disproportionately comprising people of color, in the northern central valley of

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California. In that capacity, Dr. Uzumcu regularly has patients present who are experiencing early pregnancy loss, and who request medication to complete the miscarriage. But Dr. Uzumcu is unable to provide her patients with the combined mifepristone-misoprostol regimen for early pregnancy loss because of the REMS. For years, she and her colleagues have been attempting to make mifepristone available at their health center, but the clinic administration is deeply concerned about having to require miscarriage patients to sign a form stating that they are having an abortion. As a result, Dr. Uzumcu either offers patients the misoprostol-only regimen for miscarriage—while informing them that it is less effective than the combined regimen and thus they are more likely to require an additional in-office procedure if it fails—or else must refer them elsewhere for care. Both options have significant downsides: Dr. Uzumcu's patients in the midst of a miscarriage who opt to be referred elsewhere must make an extra visit to a health center, and typically cannot obtain an appointment (even with Dr. Uzumcu's help) for three to seven days. On the other hand, if patients opt for the misoprostol-only regimen and then have the treatment regimen fail, they generally must seek an in-office dilation and curettage procedure that they were hoping to avoid. Moreover, because Dr. Uzumcu's health center does not offer that service, such patients have to travel to another facility for the procedure, often with a multi-week delay before they can obtain an appointment. If not for the REMS, Dr. Uzumcu would be able to provide

her patients with the preferred treatment regimen for medical management of miscarriage.

206. Dr. Uzumcu shares her story in her individual capacity and as a CAFP member, and not as a representative of any other institution.

207. Panna Lossy, MD, is a member of CAFP and a family medicine doctor; she also currently serves as the North Bay Chapter President for CAFP and as an alternate delegate to the CAFP board of directors. Dr. Lossy previously ran an early pregnancy options clinic within a full-spectrum primary care practice in California, where she was a certified mifepristone prescriber. She has retired from that role, but is still regularly contacted by doctors who want to integrate mifepristone into their practices and seek Dr. Lossy's help understanding and navigating the REMS barriers—including numerous such requests for help in the two months since FDA's 2023 REMS reauthorization. Doctors frequently seek out Dr. Lossy, for instance, to discuss their fears about being on an abortion provider "list," or to strategize about how they can try to reduce the burdens of REMS compliance on other departments within their health care system. Unfortunately, while Dr. Lossy can tell these colleagues that there are measures in place to try to ensure the confidentiality of mifepristone prescriber certifications, it is impossible for her to reassure them that they would not face anti-abortion violence or harassment if their certification as a mifepristone prescriber were to be leaked—especially now, post *Dobbs*. Ultimately,

even with Dr. Lossy's help, the REMS often delays or deters clinicians with whom she consults from becoming certified mifepristone prescribers.

208. While Dr. Lossy is motivated to provide this support because of her commitment to expanding safe and equitable access to reproductive health care, these conversations require time that she would otherwise spend on paid work or time with her family. Dr. Lossy does not have comparable conversations with respect to any other drug or health care service, and if FDA regulated mifepristone like other equally safe prescription drugs, these REMS-related burdens on Dr. Lossy would be eliminated.

209. Dr. Lossy shares her story in an individual capacity and as a member of CAFP and SFP, not on behalf of any other institution.

210. Additionally, SFP and CAFP each must divert resources from other organizational priorities to try to mitigate the burdens of the mifepristone REMS.

211. For instance, separate and apart from this litigation, SFP regularly participates in meetings and consults with members regarding the impact of the REMS and how to mitigate the burdens of those restrictions, and is in the process of developing guidance about seeking IRB approval for studies relating to abortion and contraception that may include a component about navigating the mifepristone REMS. These efforts require staff time and resources that SFP would otherwise spend on other clinical and policy matters relating to abortion and contraception.

212. Similarly, separate and apart from this litigation, CAFP regularly participates in meetings and consults with members regarding the impact of the mifepristone REMS and how to mitigate the burdens of those restrictions. CAFP has also engaged in specific efforts to educate its members about compliance with the REMS, for instance through a webinar. These efforts require staff time and resources that CAFP would otherwise spend on advocacy, clinical education, professional development, and other efforts to support its family physician members.

~~In addition to lacking any medical benefit, the Mifeprex REMS also significantly burdens patient access to abortion.~~

~~131. The harms the REMS causes are particularly acute for women who live in rural or medically underserved areas, have low income, are experiencing domestic abuse, and/or are young. Any or all of these factors, together with the REMS, can make it especially difficult for a woman to access abortion care.~~

~~132. Because of the Mifeprex REMS, many health care providers across the country—including Dr. Chelius and members of SFP and CAFP—cannot prescribe Mifeprex to a patient seeking medication abortion care, no matter how urgent the patient's need or the obstacles she would face in attempting to obtain timely care elsewhere.~~

~~133. In a recent, nationally representative survey of ACOG Fellows (who are currently practicing board-certified OB-GYNs), only 14% of the more than 1,100~~

respondents reported providing medication abortion care during the previous year, and those who had provided abortion care were disproportionately located in urban areas. Of the 86% of respondents who had *not* provided medication abortion care within the past 12 months, nearly one in five said that they *would* start providing such care if they could write a prescription for Mifeprex—*i.e.*, if not for the REMS.[149]

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134. There are multiple reasons why health care providers may be unable to stock Mifeprex at their clinic, office, or hospital, often stemming from ideological or political opposition to abortion within their health care facility.

135. Indeed, because of the Mifeprex REMS, even a single individual with influence over a health care facility's approval or procurement process for stocking a new drug can significantly delay, or altogether derail, a clinician's ability to prescribe Mifeprex in accordance with a patient's needs and with the provider's medical judgment. The Mifeprex REMS thus interferes with and undermines the clinician-patient relationship.

136. In addition, some health care providers, aware of the long history and ongoing threat of violence and harassment against abortion providers, are fearful of having their names included among a list of abortion providers maintained by

[149] Daniel Grossman *et al., Abortion Provision Among a National Sample of Obstetrician-Gynecologists*, 96 Contraception 273 (2017).

~~Danco and the distribution company with which it partners. Although Danco and the distribution company take significant measures to protect provider confidentiality, this concern remains an understandable deterrent to some.~~

~~137. Finally, because it typically takes several weeks for a health care provider to get certified by Danco, set up an account with the distribution company, and receive the first delivery of Mifeprex, even those health care providers who are willing to register with Danco as an abortion provider, *and* who have permission or authority to stock Mifeprex in their clinics, offices, or hospitals, will not be able to provide timely medication abortion care unless they have started this process long before a patient presents for care.~~

~~138. To set up an account with the drug distribution company, the prescriber must certify that a resolution (to become a Mifeprex dispenser) was adopted "by written consent or at a special meeting of the (circle applicable) board of directors/shareholders/managers/members/partners of said Company duly called, convened, and held in accordance with its governing documents . . ." Registrants must also provide a hard copy of their U.S. Drug Enforcement Agency license and state medical license.~~

~~139. These complicated and time-consuming logistics are not necessary for nearly any other prescription drug, and would not be necessary for Mifeprex if not for the REMS. Instead, a clinician who has diagnosed and dated an intrauterine pregnancy~~

and obtained a patient's informed consent for medication abortion care could simply write a prescription for *both* Mifeprex and misoprostol, which the patient could then fill at a local or mail-order pharmacy.

1. Plaintiff Graham Chelius, M.D.

a. Access to Abortion Care in Hawai'i

140. Numerous factors—including where a woman lives, whether she has reliable housing, how much money she earns, how old she is, whether she has children, and whether she is experiencing domestic abuse—affect her ability to access an abortion.

141. Kaua'i, the second most western of the eight main islands in Hawai'i, is one of the most remote regions in the United States. The entire island, together with the islands of Ni'ihau, Lehua, and Ka'ula (together, Kaua'i County), is federally designated as a "medically underserved area" by the Health Resources and Services Administration within HHS because of a shortage of professional health care services.

142. According to the United States Census Bureau's Supplemental Poverty Measure 2015 report, the State of Hawai'i has the ninth highest poverty rate in the nation when the state's cost of living is taken into account, with one in six people

living in poverty.[150] Because of their low household income, the majority of public school students in Kaua'i receive free or reduced-priced meals.[151]

143. Hawai'i is also the state with the highest homelessness rate in the United States,[152] and Kaua'i's homelessness rate is even higher—at 57.2 homeless per 10,000 people.[153]

144. According to the CDC's National Intimate Partner and Sexual Violence Survey published in 2017, in their lifetime, 1 in 3 women in Hawai'i have experienced sexual violence, and 2 in 5 are victims of psychological aggression by an intimate partner.[154] The State of Hawai'i Attorney General reported that in 2016 Kaua'i had an index crime rate for rape of 62.7 per 100,000 people, which is

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[150] U.S. Census Bureau, The Supplemental Poverty Measure: 2015, at 9, *available at* https://www.census.gov/content/dam/Census/library/publications/2016/demo/p60-258.pdf.

[151] David McCracken, *Over Half of Students Receive School Lunches Free or Reduced Price*, The Garden Island, March 14, 2017, *available at* http://thegardenisland.com/news/local/over-half-of-students-receive-school-lunches-free-or-reduced/article_18a6fb7d-41a0-5f8f-a8fe-e719dd546032.html.

[152] National Alliance to End Homelessness, The State of Homelessness: 2022 edition (Oct. 2022), in America 2016, https://endhomelessness.org/homelessness-in-america/homelessness-statistics/state-of-homelessness/, at 15, *available at* http://endhomelessness.org/wp-content/uploads/2016/10/2016-soh.pdf.

[153] Assuming a population estimate for the Kaua'i County of 72,029 people per the Census Bureau's latest estimates. *See* Bridging the Gap & Partners in Care, State of Hawaii Homeless Point-in-Time Count January 22, 2017, at 24, *available at* http://www.partnersincareoahu.org/sites/default/files/2017%20Statewide%20PIT%20Report%20-%20Full%20Report%20-%20FINAL.pdf.

[154] Centers for Disease Control and Prevention, The National Intimate Partner and Sexual Violence Survey 2010-12 State Report, at 33, 128, and 149, *available at* https://www.cdc.gov/violenceprevention/pdf/NISVS-StateReportBook.pdf.

almost 50% higher than the average state rate of 42.1 per 100,000 people.[155] Additionally, in 2016, the Kaua'i Police Department reported that, based on arrest data, domestic violence is the second most prevalent crime in Kaua'i.[156]

145. According to the United States Census Bureau's latest data, roughly 1 in 5 households in Kaua'i are non-English speaking.[157]

146. Hawai'i has the second-highest unintended pregnancy rate in the nation. In 2010, the last year for which data are publicly available, 56% of all pregnancies in the state were unintended, at a rate of 61 per 1,000 women ages 15-44.[158] Only one state, Delaware, has a higher unintended pregnancy rate; Hawai'i is tied with New York for second.[159]

147. According to the Guttmacher Institute, there has been a 12% decline in the number of abortion providers across Hawai'i since 2011, and a 33% decline in the number of abortion *clinics*; as of 2014, there were only four abortion clinics in the

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[155] Attorney General State of Hawai'i, 2016 A Review of Uniform Crime Reports, at v, *available at* https://ag.hawaii.gov/epja/files/2017/08/Crime-in-Hawaii-2016.pdf.

[156] Michelle Iracheta, *Domestic Violence Leads in Arrests*, The Garden Isle, January 31, 2016, *available at* http://thegardenisland.com/news/local/domestic-violence-leads-in-arrests/article_3b3e2007-0b3d-5e69-a177-34547d075879.html.

[157] U.S. Census Bureau, Selected Social Characteristics in the United States, *available at* https://factfinder.census.gov/faces/nav/jsf/pages/index.xhtml.

[158] Guttmacher Institute, State Facts About Unintended Pregnancy: Hawaii (Aug. 2017), *available at* https://www.guttmacher.org/fact-sheet/state-facts-about-unintended-pregnancy-hawaii.

[159] Guttmacher Institute, Unintended Pregnancy in the United States (Sept. 2016), *available at* https://www.guttmacher.org/fact-sheet/unintended-pregnancy-united-states.

state.[160] The majority of abortion providers in Hawai‘i are private doctors who provide care only to established patients.

148. There are no abortion providers on Kaua‘i. The nearest island with an abortion provider is on O‘ahu, which Dr. Chelius's patients can reach only by plane.

b. Dr. Chelius's Practice

149. Kauai Veterans, where Dr. Chelius works, is located in Waimea, a small town of fewer than 2,000 people on the western side of Kaua‘i. Kauai Veterans employs approximately 275 people, many of whom – like Dr. Chelius – live nearby in the Waimea area. Most members of the community have a family member, friend, or neighbor employed at the hospital.

150. Dr. Chelius practices family medicine with a focus on obstetrics at Kauai Veterans and its associated clinics, West Kauai Clinics. Since joining Kauai Veterans in January 2009, he has delivered more than 800 babies on the island.

151. In addition, Dr. Chelius serves as the Chief Medical Officer ("CMO") for the Hawaii Health Systems Corporation's Kaua‘i Region, which includes both Kauai Veterans and a second hospital on the eastern side of the island. As CMO, Dr. Chelius is primarily responsible for managing the relationship between Hawaii

[160] Guttmacher Institute, State Facts About Abortion: Hawaii (July 2017), *available at* https://www.guttmacher.org/fact-sheet/state-facts-about-abortion-hawaii.

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~~Health Systems Corporation and the physicians who serve the Kaua'i region, including participating in contract negotiations, overseeing physician staffing assignments, and responding to any complaints brought against physicians (whether by patients or staff). His position requires that he be involved in resolving most of the conflicts that arise among the small clinical team at Kauai Veterans.~~

~~152. Dr. Chelius is aware that some of his colleagues are opposed to abortion, and that they would be upset, angry, and/or uncomfortable if asked to be involved either in an abortion procedure or in the process of procuring, stocking, and dispensing Mifeprex, as required by the REMS. In addition to clinical staff, this process would likely involve staff who are responsible for hospital contracts; staff who work in the hospital pharmacy; and staff who dispense medications at West Kauai Clinics.~~

~~153. Because Dr. Chelius believes that any such request would create internal conflict, he does not provide any abortion care at Kauai Veterans or West Kauai Clinics. Instead, Dr. Chelius typically refers patients to O'ahu for care.~~

~~154. If not for the REMS, Dr. Chelius would be willing and able to write a prescription for Mifeprex for a patient seeking abortion care through ten weeks of pregnancy—without involving any of his colleagues—which the patient could then fill at one of the pharmacies on Kaua'i or via mail-order pharmacy.~~

~~***c. The Harms Dr. Chelius's Patients Experience Because of the Mifeprex REMS***~~

~~155. Traveling to O'ahu is a severe burden for Dr. Chelius's patients, particularly those with low incomes. Patients must arrange (1) transportation to the Lihue Airport on the south-eastern coast of Kaua'i, (2) a flight to O'ahu, (3) transportation from the airport in O'ahu to an abortion clinic, (4) transportation back to the airport in O'ahu from the abortion clinic, (5) a return flight to Kaua'i, and (6) transportation from the airport in Kaua'i to the patient's home. Thus, the cost of transportation alone can easily exceed $300.~~

~~156. In addition, a patient with children must also arrange for child care, which may add costs. A working patient must arrange to miss at least one day of work—which, for many low-income workers who do not have paid time off, means a day of lost wages.~~

~~157. For poor and low-income women who receive health insurance through Hawai'i's Medicaid program ("Med-Quest"), the costs of the abortion procedure and travel to obtain it are covered. However, to receive that benefit, Dr. Chelius must submit a referral and other paperwork directly to Med-Quest, which then works with the patient to arrange the travel. This process can be especially time-consuming and complicated for patients who are homeless, who do not own a~~

~~reliable cell phone, for whom English is not a first language, or who do not have reliable cell phone service because of the rural area in which they live.~~

~~158. Because of the logistics involved in this process, Dr. Chelius's Med-Quest (*i.e.*, low-income) patients typically are delayed by two to three weeks before they can leave the island to receive abortion care.~~

~~159. While abortion is extremely safe, the risks increase as pregnancy advances.~~

~~160. The cost of an abortion also increases as pregnancy advances.~~

~~161. In addition, some of Dr. Chelius's patients are delayed past the point in pregnancy at which they can obtain a medication abortion. Instead, their only options are a surgical procedure, which in many cases involves anesthesia, or carrying the pregnancy to term.~~

~~162. Medication abortion is medically indicated for certain women (*e.g.*, women with uterine anomalies), and strongly preferred by others (*e.g.*, sexual assault survivors for whom the insertion of instruments into the vagina may cause emotional and psychological trauma, or minors who have never had a pelvic exam).~~

~~163. It is especially difficult for a patient to keep her abortion decision confidential from employers, neighbors, friends, or relatives when she must fly to another island to effectuate that decision. Women in abusive relationships, whose~~

~~safety may be jeopardized if their partner is aware of their pregnancy and/or abortion, are at particular risk.~~

~~164. In addition, traveling to another island can be psychologically and emotionally taxing for some of Dr. Chelius's patients, particularly young women, women struggling with substance abuse, women for whom English is not a first language, and women who are homeless.~~

~~165. The time, costs, logistics, and emotional strain involved in traveling to O'ahu for care are insurmountable for some of Dr. Chelius's patients. Because of the REMS, some women on Kaua'i have been forced to carry a pregnancy to term against their will.~~

~~166. For the moment, a study of the efficacy and safety of medication abortion care delivered by mail is providing some temporary and imperfect relief to certain of Dr. Chelius's patients.~~

~~167. Patients participating in the study, which is not subject to the REMS, mail, fax, or email blood test and ultrasound results to a physician at the University of Hawai'i, who then meets with the patient by videoconference, obtains her informed consent, and mails her the medications. This study has allowed abortion access without flying to O'ahu for certain of Dr. Chelius's patients who have a device on which they can have a private medical conversation by videoconference at a set appointment time; a private location with reliable cell phone service in which to do~~

so; and an address where the package can be securely and confidentially mailed. For others of Dr. Chelius's patients—including those who are homeless, live in extremely remote areas, and/or need to keep their abortion decision confidential—this study offers no relief. Moreover, the study is temporary.

168. In sum, because of the Mifeprex REMS, Dr. Chelius's patients suffer significant physical, financial, and emotional harm.

2. Plaintiff Society of Family Planning

a. The Challenges SFP Members Face Because of the REMS

169. SFP members include many of the leading national experts in family planning, including abortion care.

170. Yet some of SFP's members are delayed in, or prevented from, prescribing Mifeprex to their patients because of the REMS.

171. Many SFP members work at hospitals or clinics associated with hospitals. At these facilities, as in most clinical settings, the decision to write a prescription is usually determined solely by the patient and her health care provider(s), and effectuated within the privacy of the office or examination room.

172. By contrast, in most hospitals and associated clinics, multiple layers of approval are required before a drug can be added to the hospital or clinic formulary. This often includes an individual or committee at the department level

~~(*e.g.*, the chair of the hospital's OB-GYN department); a pharmacy committee at the clinic or hospital level; and, in some cases, a pharmacy committee at the health care system level (when there is more than one hospital or clinic within the health care system). Often, these committees meet only on a periodic basis—for instance, once per quarter. Additional hospital staff, including those responsible for contract development, purchasing, and warehousing, may also be involved in the decision to procure and stock a drug.~~

~~173. This already lengthy process may be subject to additional complications when the drug in question is controversial—as is often the case with the abortion pill.~~

~~174. Because of the stigma surrounding abortion, some institutions where SFP members work have imposed additional, unique procedural hurdles to adding Mifeprex to the formulary, such as a requirement that the SFP member compile and present data on the safety of Mifeprex to the pharmacy committee.~~

~~175. Thus, in order to provide Mifeprex to their patients, some SFP members must first gain approval from dozens of people at a variety of levels within their institutions. This process is usually time-consuming, complicated, and requires SFP members to spend significant personal capital that they might otherwise put towards championing other patient health issues or advancing their careers.~~

~~176. In some cases, SFP members simply cannot get Mifeprex approved at their facility.~~

~~177. In addition, because the REMS may necessitate the involvement of additional hospital staff (such as medical assistants or hospital pharmacists) in the process of stocking or dispensing this medication, some hospitals require special staff training before allowing clinicians to start prescribing Mifeprex. For instance, a hospital may require a "values clarification training," through which health care professionals assess their own attitudes towards abortion in order to provide objective, respectful care. While this may be a beneficial service, because of the time necessary to develop and implement this training for all relevant staff, some SFP members are further delayed in their ability to prescribe Mifeprex to their patients.~~

~~178. Because of the REMS, some SFP members have been delayed by months or years in prescribing Mifeprex to their patients.~~

~~179. Because of the REMS, some SFP members have been delayed by months or years in incorporating Mifeprex into a hospital residency program, and are thus also delayed in (or prevented altogether) from training residents in the use of Mifeprex.~~

~~180. Because of the REMS, some SFP members are prevented from providing Mifeprex to their patients.~~

~~***b. The Harms SFP's Members' Patients Experience Because of the Mifeprex REMS***~~

~~181. SFP members prevented from prescribing Mifeprex because of the REMS often attempt to refer their patients elsewhere for care. For many patients, making a second trip to a second health care provider in order to obtain time-sensitive abortion care is a heavy burden because of the time and costs involved (for transportation, child care, and missed work), and because of the confidentiality risks. For women in rural or medically underserved areas, low-income women, young women, and women experiencing domestic violence, these harms are especially severe.~~

~~182. Because of the REMS, SFP members are also forced to refer long-time patients who seek to use Mifeprex—patients for whom they may have been providing obstetrical, gynecological, and/or primary care for years—to a different health care provider for abortion, even though they are qualified to provide such care themselves. This interferes with the clinician-patient relationship and can pose an additional psychological barrier to care for some patients, particularly young patients.~~

~~183. The need to make a second trip to a second health care provider delays some patients in accessing abortion care, and prevents some patients from accessing abortion care altogether.~~

~~184. Because it is challenging for some patients to travel to a different health care provider, and because of the time-sensitive nature of abortion care, some of SFP's members' patients use a method of abortion that is not as safe and effective as Mifeprex (such as using misoprostol only) or that is not their or their health care provider's preferred method (such as a surgical procedure), or are altogether prevented from accessing abortion care and instead carry a pregnancy to term against their will.~~

~~**3. Plaintiff California Academy of Family Physicians**~~

~~***a. The Challenges CAFP's Members Face Because of the REMS***~~

~~185. CAFP members are family physicians located throughout the state of California, including in rural and medically underserved areas.~~

~~186. CAFP members face many of the same barriers to prescribing Mifeprex as Dr. Chelius and the members of SFP, including opposition among colleagues to procuring, stocking, or dispensing Mifeprex at the health care facilities where CAFP members work, and complicated, multi-layer approval processes for stocking a medication at a hospital, clinic, or medical office.~~

~~187. These barriers caused by the REMS significantly delay some CAFP members in prescribing Mifeprex to patients presenting with an unwanted pregnancy.~~

~~188. In some cases, because of the REMS, CAFP members are prevented altogether from prescribing Mifeprex to their patients.~~

~~189. In addition, some of CAFP's members provide home-based care to patients who are unable to safely or comfortably travel, or who have a strong preference for privacy. Because of the REMS, CAFP members are prevented from dispensing Mifeprex to their patients at home, as they do with other medications.~~

~~190. A patient seeking abortion care may prefer to have her physician deliver her Mifeprex to her home if she is experiencing a pregnancy-related illness (such as the severe nausea and vomiting of hyperemesis gravidarum); if she does not want to walk through a gauntlet of protesters outside an abortion clinic; or if she needs to keep her abortion decision private and fears that traveling to an abortion clinic will compromise her confidentiality.~~

~~191. However, because of the REMS, CAFP members are prohibited from delivering Mifeprex directly to their patients' homes, even if that is a delivery model they regularly use for other types of care, and even if the patient is too ill to travel to the physician's office or clinic or otherwise would strongly prefer such home-based care.~~

~~***b. The Harms CAFP's Members' Patients Experience Because of the Mifeprex REMS***~~

~~192. CAFP's members' patients face similar burdens as SFP's members' patients because of the Mifeprex REMS.~~

~~193. Some are forced to make a second trip to a second health care provider for abortion care and bear the costs and emotional burdens associated with that travel.~~

~~194. Some are delayed in accessing abortion care, which increases the associated risks.~~

~~195. Some are prevented from receiving abortion care through their preferred method, and/or receive abortion care (using misoprostol alone) that is less safe and effective than the FDA-approved Mifeprex/misoprostol regimen.~~

~~196. Some are prevented from accessing abortion care altogether and instead carry a pregnancy to term against their will.~~

~~197. In addition, some are prevented from having abortion care delivered to them at home by their physician, notwithstanding their medical and/or emotional reasons for preferring to receive such care in the privacy of their home.~~

~~**4. Plaintiff Pharmacists Planning Services Inc.**~~

~~198. PPSI members include independent pharmacies and pharmacists across the state of California and in nearly all 50 states. Many PPSI members have been providing pharmacy care in their communities for years or decades and have trusted relationships with their patients.~~

~~199. Some PPSI members currently dispense misoprostol to patients for use as part of the FDA-approved two-drug regimen to terminate an early pregnancy.~~

~~200. However, because of the REMS, PPSI members are uniformly prohibited from stocking and dispensing Mifeprex.~~

~~201. The Mifeprex REMS prevents PPSI members from providing a service that is wholly within their scope of practice: dispensing prescription medication, and providing patients with information about any risks associated with the medication or its interaction with other drugs the patient is taking (in addition to the informed consent process performed by the prescriber).~~

~~202. If not for the Mifeprex REMS, some PPSI members would stock and dispense Mifeprex to patients who present with a prescription.~~

~~203. Because of the REMS, PPSI members are unable to serve their patients who need Mifeprex, which causes them to lose business.~~

~~204. Because of the REMS, some of PPSI's members' patients are delayed in accessing medication abortion care, or prevented from obtaining a medication abortion altogether.~~

CLAIMS FOR RELIEF

~~COUNT I~~

~~(Substantive Due Process – Patients' Right to Privacy)~~

~~205. The allegations of paragraphs 1 through 225 are incorporated as though fully set forth herein.~~

~~206. The Mifeprex REMS violates Plaintiff Dr. Chelius's patients' and the other Plaintiffs' members' patients' right to liberty and privacy as guaranteed by the due process clause of the Fifth Amendment to the U.S. Constitution by imposing significant burdens on abortion access that are not justified by the law's purported benefits, thereby imposing an undue burden on a woman's right to abortion.~~

COUNT I~~I~~

(Equal Protection)

~~14.~~213. The allegations of paragraphs 1 through ~~225~~ 212 are incorporated as though fully set forth herein.

~~207.~~214. The ~~Mifeprex~~ Mifepristone REMS Program violates Plaintiffs', Plaintiffs' members', and Plaintiffs' members' patients' right to equal protection of the laws under the Fifth Amendment to the United States Constitution by treating Plaintiffs, Plaintiffs' members, and Plaintiffs' members' patients differently from other similarly situated parties without a sufficient state interest.

COUNT II~~I~~

(Administrative Procedure Act: Contrary to Constitutional Right)

~~208.~~215. The allegations of paragraphs 1 through ~~225~~ 212 are incorporated as though fully set forth herein.

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~~209.~~216. ~~The~~ FDA's ~~2016~~ 2023 reauthorization of the ~~Mifeprex~~ mifepristone REMS and other agency action and inaction described herein constituted final agency action for which Plaintiffs have no other adequate remedy within the meaning of 5 U.S.C. § 704.

~~210.~~217. ~~The~~ FDA's ~~2016~~ 2023 reauthorization of the ~~Mifeprex~~ mifepristone REMS and other agency action and inaction described herein is contrary to Plaintiffs', Plaintiffs' members', and Plaintiffs' members' patients' constitutional rights, including their rights under the Fifth Amendment to the U.S. Constitution, in violation of 5 U.S.C. § 706(2)(B).

COUNT III~~V~~

(Administrative Procedure Act: In Excess of Statutory Authority)

~~211.~~218. The allegations of paragraphs 1 through ~~225~~ 212 are incorporated as though fully set forth herein.

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~~212.~~219. ~~The~~ FDA's ~~2016~~ 2023 reauthorization of the ~~Mifeprex~~ mifepristone REMS and other agency action and inaction described herein constituted final agency action for which Plaintiffs have no other adequate remedy within the meaning of 5 U.S.C. § 704.

~~213.~~220. ~~The~~ FDA's ~~2016~~ 2023 reauthorization of the ~~Mifeprex~~ mifepristone REMS and other agency action and inaction described herein is in excess of the Agency's statutory authority under the FDCA in violation of 5 U.S.C. § 706(2)(C).

COUNT IV

**(Administrative Procedure Act:
Arbitrary, Capricious, Abuse of Discretion, and Contrary to Law)**

~~15.~~221. The allegations of paragraphs 1 through ~~225~~ 212 are incorporated as though fully set forth herein.

~~214.~~222. ~~The~~ FDA's ~~2016~~ 2023 reauthorization of the ~~Mifeprex~~ mifepristone REMS and other agency action and inaction described herein constituted final agency action for which Plaintiffs have no other adequate remedy within the meaning of 5 U.S.C. § 704.

~~215.~~223. ~~The~~ FDA's ~~2016~~ 2023 reauthorization of the ~~Mifeprex~~ mifepristone REMS was not based on any reasoned decision or rational basis, and therefore was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

~~216.~~224. ~~The~~ FDA's ~~2016~~ 2023 reauthorization of the ~~Mifeprex~~ mifepristone REMS treated similarly situated entities differently without adequate justification, and therefore was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

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~~217.~~225. ~~The~~ FDA's ~~2016~~ 2023 reauthorization of the ~~Mifeprex~~ mifepristone REMS violated the Agency's governing statute and therefore is not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that the Court enter judgment in their favor and:

1) Declare, pursuant to 28 U.S.C. § 2201, that the ~~Mifeprex~~ mifepristone REMS in its entirety, as set forth above, violates the Fifth Amendment of the United States Constitution; and/or
2) Declare, pursuant to 28 U.S.C. § 2201, that certain components of the ~~Mifeprex~~ mifepristone REMS violate the Fifth Amendment of the United States Constitution:
    a. ETASU A (Prescriber ~~Special~~ Certification ~~for Prescribers~~); and/or
    b. ETASU ~~C~~ B (~~Dispensed Only in Certain Health Care Settings~~Pharmacy Certification); and/or
    c. ETASU D (Patient Agreement Form); and/or
    d. Implementation System; and/or
    e. Timetable for Assessments; and/or

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3) Declare, pursuant to 28 U.S.C. § 2201, that the ~~Mifeprex~~ mifepristone REMS in its entirety, as set forth above, violates the Administrative Procedure Act; and/or

4) Declare, pursuant to 28 U.S.C. § 2201, that certain components of the ~~Mifeprex~~ mifepristone REMS violate the Administrative Procedure Act:

   a. ETASU A (~~Special~~ Prescriber Certification ~~for Prescribers~~); and/or

   b. ETASU ~~C~~ B (~~Dispensed Only in Certain Health Care Settings~~Pharmacy Certification); and/or

   c. ETASU D (Patient Agreement Form); and/or

   d. Implementation System; and/or

   e. Timetable for Assessments; and

5) Enter an injunction prohibiting Defendants, their employees, agents, and successors in office, from requiring a REMS for Mifeprex (mifepristone), NDA 020687, mifepristone (ANDA 091178), or any future ANDA associated with these applications; and/or

6) Remand to ~~the~~ FDA with instructions to remove the ~~Mifeprex~~ Mifepristone REMS Program while maintaining the approvals of Mifeprex (mifepristone), NDA 020687, and mifepristone (ANDA 091178); and

7) Award to Plaintiffs costs, expenses, and attorneys' fees pursuant to 28 U.S.C. § 2412; and

8) Award such other, further, and different relief as the Court deems just and proper.

DATED: Honolulu, Hawai‘i, ~~October~~ March 30, 2023~~17~~.

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~~/s/ Mateo Caballero~~
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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*

Plaintiffs,

v.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIVIL ACTION

Case No. 1:17-cv-00493-JAO-RT

AMENDED AND SUPPLEMENTAL COMPLAINT

EXHIBIT 2

Plaintiffs, by and through their undersigned attorneys, bring this complaint against the above-named Defendants, their employees, agents, and successors in office, and in support thereof allege the following:

PRELIMINARY STATEMENT

1. Mifepristone is a prescription medication that U.S. patients have used for decades to end an early pregnancy by initiating a process very similar to a miscarriage.[1] As the U.S. Food and Drug Administration ("FDA" or "the Agency") observed 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]

2. Indeed, safety data from mifepristone's 5.6 million uses in the United States confirm that it is far safer than many other common medications, including Tylenol and Viagra.[3]

3. Moreover, FDA has never concluded that any very rare serious complications were actually caused by mifepristone. To the contrary, mifepristone's FDA-

[1] Plaintiffs use "mifepristone" to refer to both the brand-name drug, Mifeprex®, and its generic, mifepristone, which are subject to identical regulations.

[2] Admin. Record ("AR") 0539.

[3] U.S. Food & Drug Admin., Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2022, *available at* https://www.fda.gov/media/164331/download [hereinafter "Mifepristone U.S. Post-Marketing Adverse Events"].

approved labeling notes that the serious risks identified in mifepristone's labeling are the same risks arising any time the pregnant uterus is emptied, whether through childbirth, miscarriage, or abortion.[4] And FDA has explained that in nearly all of the (very few) cases of fatal infections associated with mifepristone, the "critical risk factor . . . is pregnancy itself."[5]

4. Nevertheless, FDA subjects mifepristone to a Risk Evaluation and Mitigation Strategy ("REMS"), which is a special set of restrictions above and beyond the normal layers of protections that apply to virtually every other prescription drug.

5. Congress permits FDA to impose a REMS *only* when "necessary to ensure that the benefits of a drug outweigh [its] risks," considering certain statutorily mandated factors. 21 U.S.C. §355-1(a)(1). Congress established further safeguards around the imposition of the most burdensome kinds of REMS—Elements To Assure Safe Use ("ETASU")—which FDA may impose only when necessary because of the "inherent toxicity or potential harmfulness" of a drug. *Id.* § 355-1(f)(1). Specifically, FDA may impose ETASU on a drug that "has been shown to be effective" only if it is "associated with a serious adverse drug experience" such that it "can be approved only if, or [approval] would be withdrawn unless, such [ETASU] are required." *Id.* § 355-1(f)(1)(A). Even then, ETASU must be

[4] AR 0398.

[5] AR 880–81 & n.69.

"*commensurate* with the specific serious risk[s]" listed in the drug's labeling, *id.* § 355-1(f)(2)(A); "required as part of [a] strategy to *mitigate*" such risks, *id.* § 355-1(f)(1)(A); and not "*unduly burdensome* on patient access to the drug, considering in particular . . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)," *id.* § 355-1(f)(2)(C) (emphases added).

6. FDA imposes a REMS on fewer than 3% of the more than 20,000 drug products it regulates, and 75% of drugs subject to a REMS are opioids[6]—which "are claiming lives at [such] a staggering rate" that they "are reducing life expectancy in the United States."[7]

7. In 2017, Plaintiffs filed this litigation challenging FDA's 2016 final agency action reauthorizing a REMS, including three ETASU, for mifepristone.

8. In 2020, a coalition of medical experts led by the American College of Obstetricians and Gynecologists ("ACOG") challenged one of the mifepristone ETASU in a separate matter: *ACOG v. FDA*, 472 F. Supp. 3d 183 (D. Md. 2020). The plaintiffs in *ACOG* argued that FDA's longstanding requirement that mifepristone be dispensed only in a hospital, clinic, or medical office was medically unnecessary and exposed patients to needless burdens and viral risks during the

[6] Joint Stip. of Facts ¶¶ 58–59 (ECF 85).

[7] *Opioid Medications*, U.S. Food & Drug Admin., https://www.fda.gov/drugs/information-drug-class/opioid-medications (last updated Mar. 29, 2021).

COVID-19 pandemic. *Id.* The U.S. District Court for the District of Maryland preliminarily enjoined this ETASU over defendants' 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. That injunction remained in place for six months. *FDA v. ACOG*, 141 S. Ct. 578, 578 (2021) (mem.) (granting stay).

9. In April 2021, FDA announced that it would exercise enforcement discretion with respect to the mifepristone in-person dispensing ETASU for the duration of the COVID-19 Public Health Emergency.[8] The Agency conceded that, during the six-month period when the in-person dispensing requirement was enjoined and mifepristone was available through mail-order pharmacies, there was *no* increase in adverse safety events.[9]

10. The next month, in May 2021, Plaintiffs in the instant case moved for summary judgment. Shortly before FDA's brief was due, the Agency notified

[8] U.S. Food & Drug Admin., REMS Review Memorandum 6 (Jan. 3, 2023) [hereinafter "2023 REMS Review"], attached hereto as Suppl. Ex. A (summarizing regulatory history).

[9] U.S. Food & Drug Admin., REMS Review Memorandum 38 (Dec. 16, 2021) [hereinafter "2021 REMS Review"], attached hereto as Suppl. Ex. B ("We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.").

Plaintiffs that it was undertaking a new review of the mifepristone REMS. On the condition that FDA would "review any relevant data and evidence submitted by the Plaintiffs," Joint Mot. Stay 2 (ECF 148), the parties jointly moved for a stay.

11. In August and September 2021, Plaintiffs submitted to FDA two letters explaining why the mifepristone REMS is medically unjustified and burdens patients and the health care system. Plaintiffs cited statements opposing the mifepristone REMS by other leading medical associations, including the American Medical Association ("AMA"), ACOG, and the American Academy of Family Physicians ("AAFP").[10] And, among other research, Plaintiffs cited data showing that after Canada eliminated its restrictions on mifepristone in 2017 to allow for normal prescribing, medication abortion remained extremely safe, with a major complication rate of only 0.33%.[11]

12. In addition, Plaintiffs gave examples of other medications that pose risks greater than or comparable to that of mifepristone but are *not* subject to a REMS. For instance, Plaintiffs noted that Jeuveau® is not subject to a REMS, even though it is used for a purely cosmetic purpose—temporarily reducing the appearance of

[10] *See generally* Letter from *Chelius* Plaintiffs to Janet Woodcock, MD (Sept. 29, 2021) [hereinafter "*Chelius* Plaintiffs' Letter"], attached hereto as Suppl. Ex. C; Letter from Soc'y of Family Planning to Christine Nguyen, MD (Aug. 13, 2021) [hereinafter "SFP Letter"], attached hereto as Suppl. Ex. D.

[11] *Chelius* Plaintiffs' Letter, *supra* note 10, at 2.

lines between one's eyebrows—and carries an FDA black-box warning for "[s]wallowing and breathing difficulties" that "can be life threatening," with "reports of death."[12]

13. In January 2023, FDA reauthorized the mifepristone REMS.[13] While permanently eliminating in-person dispensing, FDA retained the other two ETASU—including one that the Agency's own scientific review team had recommended removing in 2016 because it is "duplicative" and "does not add to safe use conditions."[14] Moreover, FDA added a *new* ETASU requiring pharmacies to become "certified" before they can dispense mifepristone—notwithstanding that pharmacies had dispensed mifepristone throughout the pandemic with no certification requirement and no increase in adverse events.

14. FDA's REMS Review memoranda reflect that, in reauthorizing the REMS in 2023, the Agency nowhere considered many of the statutory factors Congress requires to inform a decision whether to impose a REMS and ETASU, such as the "background incidence" of adverse events in the population likely to use the drug and whether the drug is a "new molecular entity" posing potentially unknown risks.

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[12] *Id.* at 3.

[13] Risk Evaluation & Mitigation Strategy (REMS) Single Shared System for Mifepristone (2023), attached hereto as Suppl. Ex. E.

[14] AR 0437, 0674.

21 U.S.C. § 355-1 (a)(1). Accordingly, the Agency never grappled with facts critical to the mifepristone REMS analysis—including FDA's admissions that continuing a pregnancy is many times more dangerous than ending a pregnancy with mifepristone and misoprostol;[15] that the risks associated with mifepristone are inherent to pregnancy and have never been shown to be caused by mifepristone rather than by pregnancy itself;[16] and that mifepristone is a very common and well-studied medication with an extremely strong and stable risk profile.[17]

15. FDA also nowhere explained how its ETASU could possibly be "commensurate" with the risks listed in the mifepristone labeling when FDA does not impose similar restrictions on other, riskier drugs. 21 U.S.C. § 355-1(f)(2)(A).

16. And FDA expressly declined to consider, *inter alia*, the positions of leading medical associations that the mifepristone REMS is not supported by science and harms patients and the health care system; and evidence showing that the mifepristone ETASU are "unduly burdensome on patient access to the drug," particularly for "patients in rural or medically underserved areas" who struggle to

[15] AR 0859 & n.6 (FDA relying on study finding that "the risk of childbirth related death was therefore approximately 14 times higher than the rate associated with legal abortion").

[16] AR 383–84, 0387, 0398.

[17] *See, e.g.*, 2021 REMS Review, *supra* note 9, at 22, 31; AR 0535 (after 15 years of mandatory adverse event reporting under the REMS, FDA "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"); AR 0574 (major adverse events associated with mifepristone are "exceedingly rare").

obtain abortion care. *Id.* § 355-1(f)(2)(C).

17. At bottom, FDA's latest REMS analyses—just like the 2016 REMS decision Plaintiffs originally challenged—assumes without supporting data that the restrictions the Agency put in place long ago, when mifepristone was still a novel drug in the United States, remain necessary after millions of uses and mountains of evidence confirming mifepristone's safety and efficacy.

18. The elimination of in-person dispensing—a decision FDA made only *after* a federal court injunction confirmed that the Agency's speculative safety concerns were unfounded—removed one key barrier that had prevented clinicians, including Plaintiff Dr. Graham Chelius, from prescribing mifepristone at all, as well as forcing countless patients to travel unnecessarily when they could otherwise safely obtain their prescription through telemedicine and by mail.

19. Nevertheless, the 2023 REMS continues to significantly impede patients' access to mifepristone—including by (1) creating an administrative morass for clinicians seeking to integrate mifepristone into their health care systems, delaying or altogether derailing their efforts to provide this care; (2) posing logistical and technological challenges that amount to a *de facto* in-person pill pick-up requirement for some patients, most often those with lower incomes; (3) deterring qualified clinicians from prescribing mifepristone because they fear anti-abortion violence and harassment if their registration as a mifepristone prescriber were ever exposed;

(4) deterring pharmacies from dispensing mifepristone because of the burdens of certification; (5) impeding research and training on mifepristone at academic institutions because of stigma arising from a REMS classification; and (6) undermining the informed consent process and provider-patient relationship by mandating counseling that is at best duplicative—and often inaccurate, confusing, and distressing.

20. In the wake of the U.S. Supreme Court's decision in *Dobbs v. Jackson Women's Health Org.*, 142 S. Ct. 2228 (2022), abortion access is decimated in much of the country and the United States faces a growing maternal mortality crisis, particularly for people of color. Against that backdrop, there is an ever more urgent need to eliminate FDA's medically unjustified restrictions on mifepristone, which needlessly reduce health care capacity and burden patients in those states where abortion access remains lawful, but is under tremendous strain.

JURISDICTION AND VENUE

21. This Court has subject matter jurisdiction over Plaintiffs' federal claims under Article III of the Constitution and 28 U.S.C. § 1331, as a civil action arising under the laws of the United States; 28 U.S.C. § 1346(a)(2), as a civil action against the federal government; 28 U.S.C. § 1343(a)(4), as a civil action to secure equitable or other relief under any Act of Congress providing for the protection of civil rights; and 5 U.S.C. § 702, as a civil action seeking judicial review of a final agency action.

22. Plaintiffs' action for declaratory and injunctive relief is authorized by 28 U.S.C. §§ 2201, 2202, and 1361, Federal Rules of Civil Procedure 57 and 65, and by the inherent equitable powers of this Court.

23. There exists an actual and justiciable controversy between Plaintiffs and Defendants requiring resolution by this Court. Plaintiffs have no adequate remedy at law.

24. This Court has authority to award costs and attorneys' fees under 28 U.S.C. § 2412.

25. Venue is proper in the District of Hawai‘i pursuant to 28 U.S.C. §§ 1391(b) and (e)(1), and 1402(a)(1), because this is a civil action in which Defendants are an agency, or officers of an agency, of the United States, because a substantial part of the events or omissions giving rise to this action occurred in the District, and because Plaintiff Chelius resides in the District.

PARTIES

A. Plaintiffs

26. Plaintiff Graham T. Chelius, M.D., is a board-certified family medicine physician with a focus in obstetrics. He works for the Hawaii Health Systems Corporation's Kaua‘i Region, which includes Kauai Veterans Memorial Hospital in Waimea, Kaua‘i, on the western side of the island ("Kauai Veterans") and Samuel Mahelona Memorial Hospital in Kapa‘a, Kaua‘i, on the eastern side of the island.

Dr. Chelius previously served as the Chief Medical Officer and Chief of Staff for the Hawaii Health Systems Corporation's Kaua'i Region. Over the past decade, he has delivered well over a thousand babies on an island of approximately 74,000 people. Dr. Chelius brings this lawsuit solely in his individual capacity and does not speak on behalf of the Hawaii Health Systems Corporation. Dr. Chelius is a resident of the State of Hawai'i.

27. The mifepristone REMS undermines Dr. Chelius's relationship with and counseling of his patients who use mifepristone, and jeopardizes his patients' privacy and safety. He sues on his own behalf and on behalf of his patients.

28. Plaintiff Society of Family Planning ("SFP") is a non-profit corporation with staff locations throughout the United States, incorporated in the state of Illinois. SFP is a national member association of clinicians, scholars, and partners united around advancing just and equitable abortion and contraception, informed by science. Membership in SFP is open to individuals who are in good professional standing and have a demonstrated interest in conducting or leveraging family planning research. Since its incorporation in 2005, SFP's membership has grown to over 1,400 members based primarily in the United States. Its members are trained in obstetrics and gynecology, internal medicine, family medicine, pediatrics/adolescent medicine, public health, demography, nursing, epidemiology, and other specialties. SFP works to advance sexual and reproductive health by providing evidence-based

insight to improve clinical care in the areas of contraception and abortion. SFP also seeks to cultivate a collaborative and supportive environment to foster scholarly activity and leadership in the areas of reproductive health and family planning.

29. SFP has members who are prevented from providing mifepristone to their patients because of the REMS. The REMS also impedes some of SFP's members from engaging in research and publication relating to mifepristone; undermines some of SFP's members' relationships with and counseling of their patients; jeopardizes the privacy and safety of some of SFP's members' patients; and prevents some of SFP's members' patients from using telemedicine to obtain mifepristone. SFP sues on behalf of its members and their patients.

30. The California Academy of Family Physicians ("CAFP") is a non-profit professional association located in San Francisco, California. With nearly 11,000 family physician, family medicine resident, and medical student members, CAFP is the largest primary care medical society in California and the largest chapter of the American Academy of Family Physicians. Since 1948, it has engaged in advocacy and education to help family physicians improve their practices and expand access to high-quality and cost-effective patient care in California. To that end, CAFP offers affordable, evidence-based continuing medical education, provides cost-saving practice management resources, and fosters opportunities to promote the family medicine specialty and ensure a strong and healthy primary care pipeline. CAFP

brings this lawsuit as an individual chapter and not as a representative of the American Academy of Family Physicians.

31. CAFP has members who are prevented from providing mifepristone to their patients because of the mifepristone REMS. The REMS also impedes some of CAFP's members from engaging in research and publication relating to mifepristone; undermines some of CAFP's members' relationships with and counseling of their patients; jeopardizes the privacy and safety of some of CAFP's members' patients; and prevents some of CAFP's members' patients from using telemedicine to obtain mifepristone. CAFP sues on behalf of its members and their patients.

B. Defendants

32. Defendant Xavier Becerra, J.D., , who is being sued in his official capacity only, is the Acting Secretary of the United States Department of Health and Human Services ("HHS") and is responsible for administering and enforcing the FDCA. In particular, the Secretary is responsible for determining, in consultation with the office responsible for reviewing a drug and the office responsible for post-approval safety with respect to a drug, whether a REMS "is necessary to ensure that the benefits of the drug outweigh the risks of the drug . . . ." 21 U.S.C. § 355-1(a)(1). The Secretary may also, in consultation with the office responsible for reviewing the drug and the office responsible for post-approval safety with respect to the drug,

require that any REMS include such ETASU as are necessary based on the drug's "inherent toxicity or potential harmfulness." *Id.* § 355-1(f)(1). Defendant Becerra maintains an office in Washington, D.C.

33. Defendant FDA is an agency of the United States Government within HHS with offices in Washington, D.C., and Silver Spring, Maryland. The Secretary of HHS has delegated to FDA the authority to administer the relevant provisions of the FDCA.

34. Defendant Robert M. Califf, M.D., who is being sued in his official capacity only, is the Commissioner of Food and Drugs and is responsible for supervising the activities of FDA, including with regard to the imposition or removal of a REMS. Defendant Califf maintains offices in Washington, D.C., and Silver Spring, Maryland.

STATUTORY FRAMEWORK

A. FDA Approval Process for New Drugs

35. Before a drug can be marketed in the United States, the drug's sponsor must submit a new drug application ("NDA") to FDA. If the NDA demonstrates that the drug is safe and effective, FDA will approve it.

36. According to FDA's website, this approval process incorporates three elements: *First*, "[a]nalysis of the target condition and available treatments," under which the Agency's reviewers

> analyze the condition or illness for which the drug is intended and evaluate the current treatment landscape, which provide the context for weighing the drug's risks and benefits. For example a drug intended to treat patients with a life-threatening disease for which no other therapy exists may be considered to have benefits that outweigh the risks even if those risks would be considered unacceptable for a condition that is not life-threatening.[28]

Second, FDA performs an "[a]ssessment of benefits and risks from clinical data." FDA explains that, "[g]enerally, the agency expects that the drug maker will submit results from two well-designed clinical trials," although "[i]n certain cases . . . convincing evidence from one clinical trial may be enough. Evidence that the drug will benefit the target population should outweigh any risks and uncertainties."[29] *Third*, FDA considers "[s]trategies for managing risks." The Agency notes: "All drugs have risks. Risk management strategies include an FDA-approved drug label, which clearly describes the drug's benefits and risks, and how the risks can be detected and managed. Sometimes, more effort is needed to manage risks. In these cases, a drug maker may need to implement a Risk Management and Mitigation Strategy (REMS)."[30]

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[28] *Development & Approval Process (Drugs)*, U.S. Food & Drug Admin., https://www.fda.gov/drugs/developmentApprovalProcess/default.htm (last updated Aug. 8, 2022).

[29] *Id.*

[30] *Id.*

37. Based on this review, the Agency either: (1) approves the drug; (2) informs the sponsor that the drug is likely to be approved once certain deficiencies in the NDA are resolved; or (3) indicates that approval cannot be obtained without substantial additional data.

38. The Agency follows a similar process in evaluating a *supplemental* NDA, in which a drug sponsor requests approval to make changes to the labeling of a previously approved drug, or to market the drug for a new indication.

39. FDA has authority under Section 506 of the FDCA (codified at 21 U.S.C. § 356) and its "Subpart H" regulations (21 C.F.R. §§ 314.500–560) to expedite approval of a new drug if it is a "promising therap[y] that treat[s] a serious or life-threatening condition and provide[s] therapeutic benefit over available therapies."[31]

40. The Agency can condition approval for an NDA on the adoption of certain safety elements (*i.e.*, ETASU), such as a restricted distribution scheme. Until 2007, FDA's primary authority to impose such elements was derived from the Subpart H regulations. However, this authority was effectively replaced by the REMS statute, described below, which was adopted as part of the Food and Drug Administration Amendments Act of 2007 ("FDA Amendments Act").

[31] *Id.*

41. Section 909 of the FDA Amendments Act states that all drugs licensed before March 2008 that were approved under Subpart H with ETASU would be automatically deemed to have an approved REMS in place. The Agency can, however, impose a REMS for any drug that fits the statutory criteria, not only those drugs originally approved under Subpart H.

B. The REMS Statute

42. The FDA Amendments Act amended the FDCA to add a new section 505-1 (codified at 21 U.S.C. § 355-1) authorizing the Secretary of HHS, in consultation with FDA's Office of New Drugs and the Office of Surveillance and Epidemiology, to impose a REMS if—and only if—"necessary to ensure that the benefits of a drug outweigh [its] risks . . . ." 21 U.S.C. § 355-1(a)(1).

43. To determine whether a REMS is necessary, the Secretary must consider six factors: (1) "[t]he estimated size of the population likely to use the drug involved," (2) "[t]he seriousness of the disease or condition that is to be treated with the drug," (3) "[t]he expected benefit of the drug with respect to such disease or condition," (4) "[t]he expected or actual duration of treatment with the drug," (5) "[t]he seriousness of any known or potential adverse events that may be related to the drug and the background incidence [*i.e.*, frequency] of such events in the population likely to use the drug," and (6) "[w]hether the drug is a new molecular entity." *Id.*

44.A REMS may include any or all of the following: a medication guide and/or patient package insert; a communication plan; and elements to assure safe usage (*i.e.*, ETASU), such as a restricted distribution scheme. *Id.* § 355-1(e)-(f).

45.ETASU are the most restrictive and burdensome type of REMS. The FDCA authorizes the Agency to impose ETASU only where "necessary to assure safe use of the drug, *because of its inherent toxicity or potential harmfulness*," *id.* § 355-1(f)(1) (emphasis added), and only if the drug is "associated with a serious adverse drug experience," *id.* § 355-1(f)(1)(A), which is defined by statute as an adverse event associated with use of the drug that results in death, the immediate risk of death, inpatient hospitalization or prolonging existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly or birth defect, or a medical or surgical intervention to prevent these outcomes, *id.* § 355-1(b)(4).

46.Moreover, FDA may impose ETASU only where "required as part of [a] strategy *to mitigate a specific serious risk*"—*i.e.*, a "serious adverse drug experience," *id.* § 355-1(b)(5)—"listed in the labeling of the drug," and the risk must be sufficiently great that FDA would not approve, or would withdraw approval for, the drug absent the ETASU. *Id.* § 355-1(f)(1)(A) (emphasis added).

47.Congress imposed several additional requirements to ensure that FDA appropriately balances such an inherently toxic drug's benefits against its "serious

risks." The ETASU requirements must "be *commensurate* with the specific serious risk[s]" listed in the drug's labeling, and may "not be *unduly burdensome* on patient access to the drug, considering in particular . . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)." *Id.* §§ 355-1(f)(2)(A), (C) (emphases added). In addition, "to the extent practicable, so as to minimize the burden on the health care delivery system," ETASU must "conform with elements to assure safe use for other drugs with similar, serious risks." *Id.* § 355-1(f)(2)(D).

48. A modification or removal of a REMS may be initiated by a "responsible person" (*i.e.*, the drug's sponsor) or by the Secretary of HHS, who may "require a responsible person to submit a proposed modification to the strategy." *Id.* §§ 355-1(g)(4)(A), (B).

49. In addition, the Secretary of HHS must "periodically evaluate, for 1 or more drugs, the [ETASU] to assess whether the elements (i) assure safe use of the drug; (ii) are not unduly burdensome on patient access to the drug; and (iii) to the extent practicable, minimize the burden on the health care delivery system." *Id.* § 355-1(f)(5)(B). Then, "considering such input and evaluations," the Agency must "modify [ETASU] for 1 or more drugs as appropriate." *Id.* § 355-1(f)(5)(C).

FACTUAL ALLEGATIONS

A. Mifepristone Regimen and Safety Record

50. The current FDA-approved regimen for the medical termination of early pregnancy involves two drugs: (1) *mifepristone* (under the brand name Mifeprex or as a generic), which interrupts early pregnancy by blocking the effect of progesterone, a hormone necessary to maintain a pregnancy, and (2) *misoprostol* (under the brand name Cytotec® or as a generic), which causes uterine contractions that expel the pregnancy from the uterus. FDA expressly authorizes misoprostol for use as part of this regimen although misoprostol's own marketing approval is only for the prevention of gastric ulcers.

51. FDA has approved the use of this regimen through 70 days (*i.e.*, 10 weeks) of pregnancy, when the overwhelming majority (more than 80%) of abortions occur.[32]

52. The FDA-approved regimen for mifepristone states that the patient initiates the abortion by taking one 200 mg tablet of mifepristone in a single oral dose on day one, and then 24–48 hours later takes four 200 mcg tablets of misoprostol buccally (*i.e.*, by placing two pills in each cheek pouch—the area between the cheek and the gums—for 30 minutes and then swallowing any remnants with water or another

[32] Katherine Kortsmit et. al., Ctrs. for Disease Control & Prevention, *Abortion Surveillance – United States, 2020*, 71 Morbidity & Mortality Weekly Report 1 (Nov. 25, 2022), https://www.cdc.gov/mmwr/volumes/71/ss/ss7110a1.htm.

liquid). The FDA-approved labeling does not specify where patients should be located when they take either medication. Most people will expel the pregnancy within 2 to 24 hours after taking the misoprostol. The patient is instructed to follow up with their health care provider approximately 7 to 14 days later to confirm that the termination of pregnancy was successful, but the FDA labeling no longer anticipates that this follow-up evaluation will occur in-person.

53. Like all medication labels, the mifepristone labeling warns about potential risks associated with the drug. Its labeling lists as risks "serious and sometimes fatal infections or bleeding."[33]

54. As FDA explained in its Summary Review Memorandum for Mifeprex in March 2016, which evaluated changes to the Mifeprex labeling and REMS, "there have been approximately 2.5 million uses of Mifeprex by U.S. women since the drug's approval in 2000."[34] During that time, FDA noted, medication abortion "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."[35] 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

[33] AR 0383–84.

[34] AR 0422.

[35] AR 0539.

marketing. Serious adverse events are rare and the safety profile of Mifeprex has not substantially changed."[36]

55. Mifepristone is also FDA-approved under the brand name Korlym® in 300 mg tablets for *daily use* by patients with endogenous Cushing's syndrome to treat high blood sugar caused by high cortisol levels in the blood. Korlym is available only from a specialty pharmacy, but it is *not* subject to a REMS. A patient's doctor submits a patient enrollment form and prescription for Korlym to a specialty pharmacy, which delivers the drug to the patient's home. The patient is then responsible for taking one to four pills (300 mg to 1200 mg, 1.5 to 6 times the recommended dose for Mifeprex) daily at home according to their prescription. In its 2016 Medical Review of Mifeprex, the Agency observed that "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."[37]

56. Mifepristone is also frequently prescribed with misoprostol as part of a regimen for medical management of early pregnancy loss. SFP, ACOG, and other leading medical associations recommend that clinicians prescribing medications to treat a miscarriage (*i.e.*, to completely evacuate the patient's uterus) utilize the

[36] AR 0681.

[37] AR 0537.

combined mifepristone-misoprostol regimen whenever mifepristone is available. But, as ACOG notes in its Practice Bulletin on Early Pregnancy Loss, while "[t]he addition of a dose of mifepristone (200 mg orally) 24 hours before misoprostol administration may significantly improve treatment efficacy . . . the availability of mifepristone is limited by the [FDA]'s Risk Evaluation and Mitigation Strategy restrictions."[38]

B. FDA Approval of Mifeprex and Imposition of the REMS

1. Initial FDA Approval

57. Mifepristone was approved for the medical termination of early pregnancy in France and China in 1988; in the United Kingdom in 1991; in Sweden in 1992; and in numerous other European countries throughout the 1990s.

58. In March 1996, the Population Council, a non-profit organization based in the United States, sponsored an 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") for the manufacturing and marketing of the medication.

59. There were three historically-controlled clinical trials on the safety and efficacy of the Mifeprex and misoprostol regimen presented to FDA as part of the

[38] ACOG, Practice Bulletin No. 200: Early Pregnancy Loss (Nov. 2018), *available at* https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/11/early-pregnancy-loss.

original NDA application, together involving 4,000 women: two trials conducted in France, which were complete at the time of the application, and one then-ongoing trial in the United States for which summary data on serious adverse events were available. The Agency 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]."[39] As part of the NDA review, 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); and (3) data on the drug's chemistry and marketing.

60. Four years later, in September 2000, FDA granted final marketing approval for Mifeprex for use in combination with misoprostol for the termination of pregnancy up to 49 days.

61. Despite the strong findings on the safety and efficacy of Mifeprex from clinical trials and European post-market experience, and despite the fact that the approval process was not expedited, the Agency approved Mifeprex under Subpart

[39] AR 0863.

H (which provides for accelerated approval—though, in fact, this four-year process was not expedited) and imposed ETASU—a restricted distribution system—as a condition of approval.

62. The ETASU imposed at the time of Mifeprex's original approval are substantively identical to the ETASU that FDA renewed in 2011 and again in 2016, described in detail *infra*.

63. According to a report by the U.S. Government Accountability Office ("GAO"), FDA stated that Mifeprex fit within the scope of Subpart H because unwanted pregnancy poses a risk of serious or life-threatening complications, Mifeprex terminates an unwanted pregnancy, and Mifeprex allows patients to avoid the risks incident to a surgical abortion procedure.[40] FDA further stated that the restricted distribution scheme was necessary to ensure patient safety, and that approving Mifeprex under Subpart H would allow FDA to impose comparable restrictions on any future generic mifepristone products.[41]

64. The Agency'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

[40] U.S. Gov't Accountability Office, *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex*, GAO-08-751, 22 (Aug. 2008), *available at* http://www.gao.gov/new.items/d08751.pdf.

[41] *Id.* at n.41.

REMS statute), only seven NDAs, including Mifeprex, were approved subject to ETASU under Subpart H.[42] By comparison, there were 961 NDAs approved in the roughly thirteen years from January 1993 to September 2005.[43]

65. Though noting its objections, the Population Council agreed to the restrictions in September 2000, and Danco began distribution of Mifeprex in November 2000. The Population Council subsequently transferred ownership of the NDA to Danco.

2. 2008 and 2011 Imposition of the Mifeprex REMS

66. In a rule released in March 2008 pursuant to the FDA Amendments Act, the Agency identified Mifeprex as one of the drugs deemed to have an approved REMS in effect because it already had ETASU in place under Subpart H. Mifeprex continued to be distributed subject to the same restrictions under which it was originally approved.

67. In 2011, FDA issued a new REMS for Mifeprex incorporating the same restrictions under which the drug was approved eleven years earlier. Specifically, the Mifeprex REMS approved in 2011 required three elements:

68. *First*, a Medication Guide to be dispensed with each Mifeprex prescription.

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[42] *Id.* at n.6, 27.

[43] U.S. Gov't Accountability Office, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49, 20 (Nov. 2006), *available at* http://www.gao.gov/new.items/d0749.pdf.

69. *Second*, the 2011 REMS included three types of ETASU (A, C, and D):

- ETASU A required clinicians to self-certify before they could prescribe Mifeprex. To be certified, the provider completed and faxed to the Mifeprex distributor a one-time Prescriber's Agreement, agreeing that they met the qualifications and would follow the guidelines outlined in the Prescriber's Agreement. These guidelines required prescribers to attest that they had the ability to date a pregnancy; had the ability to diagnose an ectopic pregnancy; had made plans for the patient to receive surgical abortion care in cases of incomplete abortion or severe bleeding, and to ensure the patient has access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and had read and understood the prescribing information for Mifeprex. In addition, the prescriber agreed to provide the patient with the Medication Guide and Patient Agreement, give her an opportunity to read and discuss them, obtain her signature on the Patient Agreement, and then sign it as well; notify the manufacturer of any cases of incomplete abortion, hospitalization, transfusion, or other serious event; and record the unique serial number on each package of Mifeprex in each patient's record.
- ETASU C restricted where a patient could receive Mifeprex once prescribed. Under ETASU C, Mifeprex could be dispensed only in certain

health care settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a prescriber specially certified under ETASU A. Mifeprex could not be dispensed through retail pharmacies.

- ETASU D placed additional requirements on the patient receiving Mifeprex. Under ETASU D, Mifeprex could be dispensed only to a patient who had completed and signed a Patient Agreement form, a copy of which was required to be placed in her medical record, and who had been provided a copy of the Medication Guide.

70. *Third*, an Implementation System, under which distributors agreed to ship the drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements; maintain secure and confidential records of shipments; and follow all distribution guidelines, including for storage, tracking, proof of delivery, and controlled returns.

71. *Fourth*, as is typical for any REMS, the sponsor was required to submit a REMS "assessment" to FDA one year from the date of the initial approval of the REMS and every three years thereafter.

3. 2016 Mifeprex Labeling Changes and REMS Assessment

a. Requested Changes to Mifeprex Label and REMS

72. Off-label use of drugs—*i.e.*, in accordance with prevailing clinical evidence, using a medication for a different indication or in a different regimen than that listed

on the FDA-approved labeling—is extremely common and widely accepted in the United States. Thus, shortly after FDA approved Mifeprex in 2000, abortion providers started prescribing the evidence-based protocol (using 200 mg of mifepristone) rather than the regimen listed on the labeling (using 600 mg of mifepristone). However, after several states banned off-label use of mifepristone—forcing patients to use an outdated regimen that was less safe and less effective than prevailing practice—in May 2015, Danco submitted a supplemental NDA to FDA proposing to update the labeling to reflect evidence-based practice across the country. In July 2015, Danco also submitted its statutorily required REMS assessment, proposing minor modifications to the REMS (primarily to ensure that the language used in the prescriber and patient agreement forms reflected the proposed changes to the labeling).

73. This submission prompted a top-to-bottom review of the Mifeprex labeling and REMS by FDA in 2015-2016. As part of that review, the Agency stated that it considered three letters submitted by more than 40 medical experts, researchers, advocacy groups, and professional associations—including Plaintiff SFP—who asked, *inter alia*, that the REMS be eliminated.

74. Other signatories requesting that FDA eliminate the Mifeprex REMS included ACOG, the leading professional association of physicians specializing in the health care of women, which represents more than 60,000 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; and the Senior Research Demographer in the Office of Population Research at Princeton University.

75. The Agency's March 2016 Cross Discipline Team Leader Review Memorandum for Mifeprex ("2016 Team Leader Review"), in a section entitled "Advocacy Group Communications," noted:

> The Agency received three letters from representatives from academia and various professional organizations, including [ACOG], [APHA], the National Abortion Federation (NAF), Ibis Reproductive Health and Gynuity [Health Projects]. 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*. (emphasis added).[44]

[44] AR 0465.

76. In FDA's 2016 Medical Review, in a section entitled "Methods," the Agency further noted: "Articles were also cited in three letters sent to [Center for Drug Evaluation and Research] 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."[45]

77. Director Woodcock also directly acknowledged receipt of the letter submitted by thirty professional and academic organizations, including Plaintiff SFP. In a February 25, 2016, letter addressed to the individual serving as the liaison for those groups, she wrote:

> Thank you for your letter dated February 4, 2016, to [then-Acting FDA Commissioner] Dr. Ostroff, Dr. Califf, and me with recommendations to lift the Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex (mifepristone), and to extend the indicated use of Mifeprex through a gestational age of 70 days. Dr. Ostroff has asked me to respond on behalf of the FDA because the Center for Drug Evaluation and Research is responsible for regulating all drugs, including mifepristone. Please share this response with your cosigners. In your letter, you strongly encouraged FDA to revise the mifepristone label and eliminate the REMS restrictions, especially the Elements to Assure Safe Use [ETASU] . . . . You also recommended not restricting the location where the patient should take these drugs . . . . Moreover, you proposed that any licensed health care provider should be able to prescribe mifepristone, and that it be available through pharmacies

[45] AR 0550.

> as well as provider offices. Your letter has been shared with the appropriate FDA staff and will be carefully reviewed.[46]

78. The letter submitted by Plaintiff SFP argued, *inter alia*:

> 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 and that serious complications are rare. 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 . . . . 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 . . . . As policy, advocacy, social science, research, and academic organizations, we ask the FDA to consider the substantial evidence presented in the [letter previously submitted by academic professionals and women's health non-profit organizations], 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, 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.[47]

[46] AR 1265.

[47] AR 1254.

79. SFP's letter also explained in detail why the Mifeprex REMS with ETASU harms patient access to Mifeprex. In particular, SFP's letter stated that ETASU C, which restricted where Mifeprex could be dispensed, "significantly curtails mifepristone's potential to expand patient access to abortion care" because it "[is] a burden to providers and, therefore, deter[s] some health care providers from offering medication abortion."[48] They explained:

> 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 . . . . [T]he majority of people who seek abortion care are already in difficult financial situations, and are disproportionately people of color. Costly and unnecessary visits to the doctor significantly increase financial and logistical burdens for these individuals and communities.[49]

80. SFP's letter explained why ETASU A, the Prescriber's Agreement, "is unnecessary for the safe dispensation of mifepristone," noting, *inter alia*, that "health care professionals are already subject to many laws, policies, and ordinary

[48] AR 1255.

[49] AR 1255–56.

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."[50]

81. SFP and the other signatories further argued that 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.[51]

[50] AR 1256. According to FDA, a "boxed" or "black box warning" "appears on a prescription drug's labeling and is designed to call attention to serious or life-threatening risks." U.S. Food & Drug Admin., Consumer Health Information, *A Guide to Drug Safety Terms at FDA* 2 (Nov. 2012), *available at* https://www.fda.gov/downloads/forconsumers/consumerupdates/ucm107976.pdf.

[51] AR 1256.

82. The letter also noted that "[t]he Prescriber's Agreement would be incompatible and unnecessary if there were an expanded distribution system."[52]

83. Finally, the letter requested that the Agency remove ETASU D, the Patient Agreement, which is "medically unnecessary and interferes with the clinician-patient relationship."[53]

b. FDA's 2016 Approval of Revised Label

84. FDA adopted nearly all of Danco's proposed labeling changes (discussed *supra* at ¶ 72), including reducing the recommended dosage of mifepristone from three 200 mg tablets to one 200 mg tablet and removing the reference to the patient's follow-up assessment—to assure completion of the abortion seven to fourteen days after taking the mifepristone—as an in-person examination.

85. FDA also approved two changes regarding where the patient takes the mifepristone and misoprostol. First, the labeling no longer stated that the patient takes the mifepristone and misoprostol "at [their] provider's office." Rather, although health care providers were still required to *dispense* the Mifeprex only in certain medical facilities according to the REMS, the updated labeling no longer specified where they *take* the pill; it simply stated that the patient takes the

[52] *Id.*

[53] AR 1257.

mifepristone in a single oral dose on "Day One," and then takes four tablets of misoprostol by the buccal route 24-48 hours later.[54] The labeling advises the health care provider to "discuss with the patient an appropriate location for her to be when she takes the misoprostol, taking into account that expulsion [*i.e.*, the miscarriage] could begin within 2 hours of administration."[55]

86. In addition, the labeling clarified that mifepristone can be safely used through 70 days of pregnancy (rather than 49).[56] The Agency concluded in its 2016 Medical Review that, based on the scientific evidence, "[m]edical termination of pregnancies through 70 days gestation is safe and effective and should be approved."[57]

c. FDA's 2016 Reauthorization of the REMS

87. As part of its review of the proposed labeling changes, the Agency undertook to "assess[] the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks."[58] This assessment was conducted by a multidisciplinary reviewing team and elevated to the Commissioner of FDA, a political appointee—Defendant Robert Califf, who

[54] AR 0385.

[55] *Id.*

[56] AR 0383, 0384, 0391, 0399.

[57] AR 0548.

[58] AR 0375.

would later also helm FDA at the time of the 2023 REMS updates—who gave specific feedback on proposed changes to the Mifeprex REMS.

88. FDA reviewers met on January 15, 2016, "to discuss proposed revisions to the REMS," and the Agency's review process was documented in detail in at least seven internal memoranda (attached to Plaintiffs' original complaint as Exhibits A, C-F, J-K). In evaluating each element of the REMS, the Agency considered, *inter alia*, "safety data gathered over the past 16 years since approval, and information regarding current clinical practice."[59]

89. Following this comprehensive review, the Agency "determined that a REMS continues to be necessary to ensure the safe use of Mifeprex," and reauthorized the REMS program, including all of the ETASU, with only minor modifications.[60]

90. The reauthorization of the REMS in March 2016 constituted a final agency action. It marked the consummation of the Agency's decision-making process and was a decision from which legal consequences flowed.

91. The Agency made the following modifications to the REMS: (1) revisions to the language in the Prescriber's Agreement form; (2) removal of the Medication Guide as a REMS element; (3) updating of the REMS goals to reflect these changes;

[59] AR 0702.

[60] AR 0849.

and (4) removal of the additional adverse event reporting requirements, other than with respect to deaths.[61] The stated goal of the 2016 Mifeprex REMS program was "to mitigate the risk of serious complications associated with Mifeprex by: (a) Requiring health care providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program[,] (b) Ensuring that Mifeprex is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber[,] [and] (c) Informing patients about the risk of serious complications associated with Mifprex."[62]

92. The Agency's multidisciplinary team of reviewers had also recommended eliminating ETASU D, the Patient Agreement form, because they concluded that it was no longer necessary. As Director Woodcock explained in a March 28, 2016, internal memorandum, Agency staff "found that the information contained in the Patient Agreement Form [required by the REMS] 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."[63] Agency reviewers observed that "[i]t is standard of care for patients undergoing pregnancy termination to undergo extensive

[61] AR 0680–81; *see also* AR 0688.

[62] AR 0404.

[63] AR 0674.

counseling and informed consent,"[64] and noted that "FDA has removed REMS requirements in other programs based on the integration of the REMS safe use condition into clinical practice."[65] The Agency's 2016 Summary Review "concur[red] 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*."[66]

93. However, "[a]fter being briefed on the planned changes to the NDA that the Center [for Drug Evaluation and Research] was considering, the Commissioner [of FDA] . . . requested that the Patient Agreement Form be retained as an element of the REMS."[67] Therefore, Director Woodcock "asked [Agency staff] to include a Patient Agreement Form in the REMS for Mifeprex," which they did.[68]

94. It is extremely rare that the FDA Commissioner, a political appointee, would weigh in on a REMS assessment. This unusual interference is consistent with the Agency's conduct denying the application to make Plan B® (commonly known as "the morning after pill"), which is used to prevent pregnancy, available over-the-counter with no age restrictions—where the U.S. District Court for the Eastern

[64] AR 0437.

[65] AR 0465.

[66] AR 0437.

[67] AR 0674.

[68] *Id*.

District of New York found "overwhelming evidence of political pressure underlying the agency's actions." *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 166 (E.D.N.Y. 2013) (finding that FDA did not have authority to mandate point-of-sale restrictions on levonorgestrel-based emergency contraception given the scientific data demonstrating that adolescents could safely use Plan B).

d. Events Post-Dating Plaintiffs' Filing

95. In October 2017, Plaintiffs filed the instant matter.

96. In 2019, FDA approved a generic version of mifepristone with substantively identical labeling, and established a single, shared system REMS encompassing both Mifeprex and the generic version that is substantively identical to the REMS approved for Mifeprex in 2016. The single, shared system REMS is known as the Mifepristone REMS Program.[69]

97. In March 2020, in response to the COVID-19 pandemic, Defendants FDA and HHS took extraordinary measures to promote the use of telemedicine and reduce the need for in-person health care visits, in order to mitigate viral exposure risks. For instance, FDA issued guidance declaring its intention not to enforce REMS requirements for in-person laboratory testing for the duration of the public health emergency, and the Secretary of HHS activated an emergency exception allowing

[69] 2023 REMS Review, *supra* note 8, at 6.

health care providers to prescribe controlled substances, including opioids, via telemedicine without first conducting an in-person examination.[70]

98. Leading medical associations and health care providers asked FDA to likewise exercise enforcement guidance with respect to the in-person dispensing ETASU for mifepristone.[71] But FDA left that restriction in place, offering no explanation for its constructive denial—and continuing its singular treatment of mifepristone.

99. In May 2020, ACOG led a coalition of plaintiffs in a challenge to the mifepristone in-person dispensing ETASU in the U.S. District Court for the District of Maryland, resulting in a preliminary injunction that blocked enforcement of this requirement for the six months the injunction was in place, and for the first time enabled mifepristone patients to obtain their medication from a mail-order pharmacy. *ACOG v. FDA*, 472 F. Supp. 3d 183 (D. Md. 2020), *stayed*, 141 S. Ct. 578 (2021) (mem.).

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[70] U.S. Food & Drug Admin., Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency: Guidance for Industry and Health Care Professionals (Mar. 2020), https://www.fda.gov/media/136317/download; *COVID-19 Information Page, Telemedicine*, U.S. Drug Enf't Admin., https://www.deadiversion.usdoj.gov/coronavirus.html#TELE (last visited Mar. 30, 2023).

[71] *See, e.g.*, Letter from Maureen G. Phipps, MD, MPH, FACOG, Judette Louis, MD, MPH, and Matt J. Granato, LLM, MBA, to Stephen M. Hahn, MD (Apr. 20, 2020), attached hereto as Suppl. Ex. F.

100. On April 12, 2021, FDA announced that it intended to exercise enforcement discretion for the remainder of the COVID-19 Public Health Emergency with respect to the mifepristone in-person dispensing requirement.[72]

101. On April 16, 2021, Plaintiffs moved for summary judgment in the instant matter. Shortly thereafter, FDA informed Plaintiffs that it was comprehensively reviewing the mifepristone REMS. On the condition that FDA would also "review any relevant data and evidence submitted by the Plaintiffs," Joint Mot. Stay 2 (ECF 148), the parties jointly moved for a stay, which this Court granted on May 7, 2021. As FDA explains in its Frequently Asked Questions for mifepristone, this litigation was the catalyst for its REMS Review: "The agency's comprehensive review of the Mifepristone REMS Program, which led to the agency's December 16, 2021, decision that a modification is required, was related to the litigation in *Chelius v. Becerra*."[73]

[72] 2023 REMS Review, *supra* note 8, at 6.

[73] *Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation*, U.S. Food & Drug Admin. (last updated Jan. 4, 2023), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation (answer to question 29, under "Litigation and Other Legal Issues"; *accord id.* (answer to question 35, under "The January 2023 REMS Modification").

102. In May 2021, FDA approved a supplemental new drug application seeking to modify the Patient Agreement Form for mifepristone to reflect gender-neutral language.[74]

103. In August and September 2021, Plaintiffs submitted to FDA two letters containing evidence demonstrating that the mifepristone REMS is medically unnecessary and burdensome on patients (especially patients who face difficulties accessing health care) and on the health care delivery system itself. For instance, Plaintiffs' letters included:

- Statements opposing the mifepristone REMS by other leading medical associations, including the American Medical Association ("AMA"), ACOG, and the American Academy of Family Physicians ("AAFP").[75]

- Specific examples of other medications posing risks greater than or comparable to that of mifepristone that are *not* subject to a REMS.[76]

- A study abstract showing that after Canada eliminated its restrictions on mifepristone in 2017 to allow normal prescribing, medication abortion remained extremely safe, with a major complication rate of 0.33%.[77]

- Sworn testimony from seven physicians in different states detailing how the mifepristone REMS prevented or substantially delayed them and other doctors they know from prescribing mifepristone, impeding patients' access. For instance, Dr. Joey Banks cited specific examples of physicians who have told her that the reason they do not provide mifepristone is because they are

[74] 2023 REMS Review, *supra* note 8, at 5.

[75] *Chelius* Plaintiffs' Letter, *supra* note 10, at 1.

[76] *Id.* at 3.

[77] *Id.* at 2.

"worried" about being placed "on a list of abortion providers."[78] Dr. Charisse Loder explained how it took years to make mifepristone available at the University of Michigan's Women's Clinic, including because of "concerns that the University would face legal liability if clinicians who were not acting pursuant to a REMS prescriber agreement prescribed this drug," which a special taskforce spent "many meetings" discussing.[79] Dr. Jane Roe discussed how the patient agreement "actively *undermines* my informed consent process by forcing me to discuss with my patients information that is inconsistent with my clinical approach and increasingly out-of-step with the research on Mifeprex as science moves forward," for instance by requiring patients to attest that they are having an abortion even if they are in fact using the medication to treat a miscarriage.[80]

- An analysis from a leading national expert in poverty and women's welfare regarding how the REMS reduces patients' access to mifepristone, particularly for patients with lower incomes and patients living in rural and medically underserved areas.

104. Other leading medical professional associations, such as ACOG, also submitted their own letters opposing the REMS. For instance, in a letter submitted on October 6, 2021, ACOG noted that "[t]he REMS and ETASU requirements for mifepristone are inconsistent with those for other medications with similar safety profiles, and create barriers to access without demonstrated improvements to patient safety or outcomes."[81]

[78] *Id.* at App. 040–41.

[79] *Id.* at App. 066–69.

[80] *Id.* at App. 084–85 (emphasis in original).

[81] Letter from Maureen G. Phipps, MD, MPH, FACOG, to Janet Woodcock, MD (Oct. 6, 2021), attached hereto as Suppl. Ex. G.

105. FDA's 2021 REMS Review memorandum states that the agency's review encompassed a search of published literature through July 26, 2021, as well as "safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants [*i.e.*, Danco and GenBioPro, which manufactures the generic]." FDA's "review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below."[82]

106. In fact, FDA expressly omitted from its analysis much of the data and evidence provided by the *Chelius* Plaintiffs. FDA refused to consider, *inter alia*, "[i]nformation from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, *even if the study assessed REMS ETASUs*," "[o]pinions, commentaries, or policy/advocacy statements," and "[d]ata on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care."[83] FDA refused to consider this information even though it is relevant to whether a REMS is "necessary" for mifepristone; whether the mifepristone ETASU are "commensurate with the specific serious risk[s]" listed in

[82] 2021 REMS Review, *supra* note 9, at 4.

[83] *Id.* at 11–12 (emphasis added).

the drug's labeling, and/or "unduly burdensome on patient access to the drug, considering in particular . . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)"; and whether the ETASU "conform with elements to assure safe use for other drugs with similar, serious risks" "so as to minimize the burden on the health care delivery system." *Id.* §§ 355-1(a)(1), (f)(2)(A), (C), (D).

107. On December 16, 2021, FDA completed its review of the Mifepristone REMS Program and determined that it would: retain the REMS Program; retain the prescriber certification ETASU; retain the patient agreement ETASU; remove the in-person dispensing ETASU; and add a new pharmacy certification ETASU. FDA sent REMS Modification Notification letters to the two drug application holders notifying them that the REMS Program must be retained with these modifications.

108. In June 2022, the drug application holders submitted supplemental new drug applications consistent with FDA's REMS Modification Notification letters. Over the following months, the application holders held several meetings with FDA, responded to information requests by the Agency, and submitted several amendments to their supplemental applications.

109. On January 3, 2023, FDA completed a subsequent review memorandum ("2023 REMS Review") and released an updated REMS for mifepristone. This constituted a final agency action. It marked the consummation of

the Agency's decision-making process and was a decision from which legal consequences flowed.

C. The Mifepristone REMS Confers No Benefit on Patients and Does Not Satisfy the Statutory Requirements for a REMS with ETASU

1. A REMS is Not Necessary to Ensure That the Benefits of Mifepristone Outweigh Its Risks

110. The FDCA allows the Agency to impose a REMS 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). None of the six factors the Secretary is statutorily required to consider in making this determination supports FDA's decision to reauthorize the Mifepristone REMS Program in 2023:

111. **"The estimated size of the population likely to use the drug involved,"** 21 U.S.C. § 355-1(a)(1): Since Mifeprex's approval in 2000 for use in the United States, medication abortion has, the agency noted, "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."[84] Between September 2000 and 2022, mifepristone had been used 5.6 million times in the United States..

[84] AR 0539.

112. Statutory guidance released by FDA in April 2019 states that, in applying this REMS factor, FDA "considers, among other things, the extent to which that population includes patients expected to use the drug for unapproved uses and the risks associated with those uses."[85] But unlike opioids, which comprised approximately 75% of REMS drugs as of 2019,[86] patients use mifepristone only for its labeled indication—ending a pregnancy—or for other evidence-based reproductive health care like miscarriage care.

113. Many more people could potentially benefit from mifepristone. Indeed, the Guttmacher Institute has found that one in four women in the United States will have an abortion during her lifetime, and as SFP observed in its letter to the Agency, "[t]he steady increase in use of medication abortion . . . shows that many women prefer this option, and that it has the ability to improve access to abortion, even in states with restrictive laws." [87]

114. Because mifepristone has already been safely used by millions of U.S. patients for its approved indication or for another safe, evidence-based regimen

[85] U.S. Food & Drug Admin., *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary Guidance for Industry* 9 (Apr. 2019), *available at* https://www.fda.gov/media/100307/download [hereinafter "FDA Statutory Factor Guidance"].

[86] Joint Stip. of Facts ¶ 59.

[87] AR 1254.

endorsed by leading medical authorities like SFP and ACOG, and because increasing access to this medication would help many more, this factor weighs against a REMS.

115. **"The seriousness of the disease or condition that is to be treated with the drug,"** 21 U.S.C. § 355-1(a)(1): The Agency acknowledges that pregnancy is a serious condition. In a 2016 denial of a citizen petition seeking to withdraw FDA approval for mifepristone, FDA explained:

> Pregnancy can be a serious medical condition in some women. 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. 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. According to the Institute of Medicine, women experiencing an unintended pregnancy may experience depression, anxiety, or other conditions.[88]

[88] AR 0859.

116. Because mifepristone treats a serious condition, and thus offers a substantial potential benefit, this factor weighs against a REMS.

117. **"The expected benefit of the drug with respect to such disease or condition,"** 21 U.S.C. § 355-1(a)(1): In denying the citizen petition asking the Agency to withdraw the mifepristone approval, FDA—on the same day that it reauthorized the REMS—further explained: "[M]edical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion."[89] For instance, in one of the clinical studies conducted in the U.S. shortly before Mifeprex's approval,

> medical termination of pregnancy avoided an invasive surgical procedure and anesthesia in 92 percent of the [study participants]. 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.[90]

118. In addition, some people prefer medication abortion because it feels more natural, and allows them to pass the pregnancy in the privacy and comfort of

[89] AR 0860.

[90] *Id.*

their home. Indeed, in its 2016 Medical Review, the Agency noted that "[t]he studies [supporting the Mifeprex labeling changes], *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."[91] In short, mifepristone allows patients to have an abortion in a private, comfortable, and safe location, on their own terms.

119. While misoprostol also has abortifacient properties acting alone, the combined regimen of mifepristone and misoprostol is the preferred regimen for medication abortion care and the most common regimen for medication abortion care in the United States; and is associated with fewer side effects than the misoprostol-only treatment.

120. Because the benefits that mifepristone offers to patients seeking to end an unwanted pregnancy without surgical intervention are significant and well-established, this factor weighs against a REMS.

121. **"The expected or actual duration of treatment with the drug,"** 21 U.S.C. § 355-1(a)(1): mifepristone is a single 200 mg tablet that is only prescribed for a single use. Korlym, by contrast, is an identical product prescribed for chronic, daily use in dosages ranging from 300 to 1200 mg. Korlym is not subject to a REMS;

[91] AR 0589.

it is delivered to the patient's home, and the patient is expected to take up to four pills daily per physician instruction. The label includes a boxed warning that Korlym may have abortifacient effects and that patients should not use it if they are pregnant,[92] and the Agency trusts patients to use it accordingly.

122. Because mifepristone is prescribed as a single tablet and poses virtually no risk of misuse, whereas an identical drug that is prescribed in higher doses for daily home administration is not subject to a REMS, this factor weighs against a REMS.

123. **"The seriousness of any known or potential adverse events that may be related to the drug and the background incidence [*i.e.*, frequency] of such events in the population likely to use the drug,"** 21 U.S.C. § 355-1(a)(1): By FDA's own admission, major adverse events associated with mifepristone are "exceedingly rare, generally far below 0.1% for any individual adverse event."[93] Accordingly, the Agency concluded in March 2016 that it was appropriate to *remove* the requirement that Danco report any hospitalizations, blood transfusions, or other serious events relating to Mifeprex other than death, as the "FDA has received such reports for 15 years, and it has determined that the safety profile of Mifeprex is well-

[92] AR 0269.

[93] AR 0574.

characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely."[94]

124. Similarly, in December 2021, FDA confirmed that "[o]ur review of [mifepristone's] postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced."[95]

125. Mifepristone's FDA-approved labeling explains that "[n]o causal relationship between the use of [mifepristone] and [serious or fatal infections or bleeding] has been established."[96] To the contrary, the FDA-approved Mifepristone Medication Guide acknowledges that the risks listed in the labeling are not inherent to mifepristone, but rather are risks associated with emptying a pregnant uterus by any means: "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

[94] AR 0535.

[95] Letter from Patrizia Cavazzoni, MD, to Donna J. Harrison, MD & Quentin L. Van Meter, MD, FCP, Re: Docket No. FDA-2019-P-1534 26 [hereinafter "2021 AAPLOG Pet. Denial"], attached hereto as Suppl. Ex. H; *accord* 2021 REMS Review, *supra* note 9, at 22.

[96] AR 384; *accord* AR 387, 398.

abortion, or *childbirth*." (emphasis added).[97] In other words, there is a relatively *high* background incidence of such adverse events among pregnant people generally.[98]

126. Moreover, the Agency acknowledges that "data from the medical literature and findings by the [U.S. Centers for Disease Control and Prevention ("CDC")] suggest that the critical risk factor" in nearly all of the few cases of fatal infections associated with mifepristone "is pregnancy itself," because similar infections "have been identified both in pregnant women who have undergone medical abortion and those who have not[.]"[99]

127. FDA's 2016 Medical Review also expressly concluded that "[m]edical abortion in adolescents appears to be at least as safe, if not safer, as in adult women."[100]

128. Because numerous studies and over two decades of clinical data in the United States confirm that mifepristone is safe—and that serious adverse events are rare, decreasing, and never shown to have been caused by mifepristone—this factor weighs against a REMS.

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[97] AR 383; *accord* AR 0398.

[98] AR 0398 ("[R]arely, serious and potentially life-threatening bleeding, infections, or other problems can occur *following a miscarriage, surgical abortion, medical abortion, or childbirth*." (emphasis added)); *accord* 2021 AAPLOG Pet. Denial, *supra* note 95, at 36.

[99] AR 0880–81 & n.69.

[100] AR 0603.

129. **"Whether the drug is a new molecular entity,"** 21 U.S.C. § 355-1(a)(1): Mifepristone is not a new molecular entity. Mifepristone has been marketed in the United States since 2000, with no new safety concerns since 2005.[101] "Available information about" mifepristone is far from "limited," and there is no "uncertainty about risks associated with the use of the drug that might emerge in the post-approval setting."[102] Because mifepristone is a well-known compound, this factor weighs against a REMS.

130. Finally, because none of these factors supports maintaining the Mifepristone REMS Program, the implementation system and timetable for assessments from the drug manufacturer also are unnecessary. Indeed, as FDA's 2016 Medical Review acknowledged, even without a REMS, "the [drug manufacturer] 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."[103]

[101] AR 0354.

[102] FDA Statutory Factor Guidance, *supra* note 85, at 8.

[103] AR 0535.

2. The Mifepristone ETASU Are Not "Commensurate With" and Do Not Mitigate the "Specific Serious Risk[s]" Listed in the Labeling.

131. In violation of the FDCA, the mifepristone ETASU are not "commensurate with the specific serious risk[s]" listed in the labeling, 21 U.S.C. § 355-1(f)(2)(A), which are "[s]erious and sometimes fatal infections or bleeding."[104] To the contrary, the ETASU are disproportionate to, have no nexus with, and will not mitigate, the risks listed in the labeling.

132. Moreover, drugs whose risks are similar to or greater than those of mifepristone are not subject to comparable restrictions.

a. The Mifeprex ETASU Are Disproportionate Because Serious Adverse Events Are "Exceedingly Rare"

133. The Agency concedes that serious adverse events associated with Mifeprex are "exceedingly rare."[105] In its 2016 Medical Review, the Agency concluded: "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 [revised] 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

[104] AR 0383.

[105] AR 0574.

events appears to have remained steady over time, with a possible decrease in severe infections."[106]

134. Similarly, as detailed *supra* ¶ 124, FDA found in 2021 that serious adverse events remained very low even when the in-person dispensing ETASU was eliminated, notwithstanding FDA's insistence from 2000 until April 2021 that this requirement was essential for safe use.

135. In the nearly 22 years of U.S. post-marketing data available to FDA when it reauthorized the REMS in 2023, there were only 28 reported associated deaths out of 5.6 million uses—an associated fatality rate of 0.0005%.[107] By contrast, the fatality rate associated with phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction (*e.g.*, Viagra), which are not subject to a REMS, is estimated at 0.0026% of users, roughly 5 times the mifepristone-associated mortality rate.[109]

136. At least 9 of the reported deaths in women who had taken mifepristone involved events clearly unrelated to the medication: narcotic overdose or suspected

[106] AR 0611.

[107] AR 0609–10.

[109] Gregory Lowe & Raymond A. Costabile, *10-Year Analysis of Adverse Event Reports to the Food and Drug Administration for Phosphodiesterase Type-5 Inhibitors*, 9 J. Sex. Med. 265, 268-69 (2012).

homicide.[110] And FDA acknowledges that "[t]here is no information that use of Mifeprex and misoprostol caused" the "very small number" of deaths from infection.[111] Rather, as explained *supra* ¶¶ 125–26, CDC findings and the medical literature suggest that pregnancy itself, not Mifeprex usage, was the "critical risk factor" in nearly all of the (very few) cases of fatal infection.[112]

137. Indeed, as FDA acknowledges, a woman is at least 14 times more likely to die if she carries a pregnancy to term than if she uses mifepristone to end a pregnancy.[113] Moreover, the two risks listed in the mifepristone labeling are 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").

b. The ETASU Do Not "Mitigate" the Risks Listed in the Mifepristone Labeling

138. An essential flaw in the Mifeprex REMS is that there is no nexus between the risks listed on the Mifeprex label and the ETASU—they do not serve to "mitigate" any such risks, as required by 21 U.S.C. § 355-1(f)(1)(A). Specifically:

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[110] Mifepristone U.S. Post-Marketing Adverse Events, *supra* note 3, at 1.

[111] AR 0261.

[112] AR 0880– 81 n.69.

[113] AR 0859 & n.6 (citing 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)).

i. ETASU D: Patient Agreement

139. Every one of the FDA experts who participated in the Agency's formal March 2016 review for Mifeprex concluded that the Patient Agreement provides no medical benefit.

140. Those unanimous conclusions were amended only after defendant Commissioner Robert Califf requested that this ETASU be maintained nonetheless. The sole rationale for the Commissioner's unusual intervention is documented in a memorandum from Director Woodcock, in which she states that "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."[115]

141. Commissioner Califf made this request notwithstanding that medication abortion does not involve any "procedure," only pills, and notwithstanding that FDA's 2016 Summary Review "concur[red] with the clinical review team that the Patient Agreement Form, which requires a patient's signature,"

[115] AR 0674.

is duplicative of existing informed consent laws and standards, "does not add to safe use conditions for the patient for this REMS[,] and is a burden for patients."[116]

142. In its 2021 review, FDA "agree[d] that informed consent in medicine is an established practice" as a general matter,[117] and specifically found that a survey of abortion providers in the United States and Canada in 2017 "did reveal strong adherence to evidence-based guidelines."[118]

143. Nevertheless, FDA noted that "removal of the in-person dispensing requirement could significantly increase the number of [mifepristone] providers to a larger group of practitioners,"[119] and reasoned that the Patient Agreement ETASU will ensure that "each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care."[120]

144. FDA offered no explanation at all for why a special counseling form is necessary to ensure adequate counseling by new prescribers with respect to the use, risks, and follow-up care for mifepristone—a medication with a well-established risk profile, which has been available in the United States for nearly a quarter of a

[116] AR 0437, 0674.

[117] 2021 REMS Review, *supra* note 9, at 17.

[118] *Id.*

[119] *Id.* at 18; *accord id.* at 37; 2023 REMS Review, *supra* note 8, at 11– 12.

[120] 2021 REMS Review, *supra* note 9, at 18.

century—when FDA approves *entirely new drugs* all the time without a patient agreement form, even though *every* prescriber will be unfamiliar with that novel medication.

145. Moreover, mifepristone already has a special "medication guide" as part of its labeling that discusses mifepristone's use, risks, and follow-up care. The 2016 FDA review team specifically found the patient agreement form "duplicative" of the mifepristone medication guide, which "contains the same risk information covered under the Patient Agreement form,"[121] using patient-friendly language.[122] Yet FDA nowhere addressed this duplication in its 2021 or 2023 reviews.

ii. ETASU A: Special Certification for Prescribers

146. To become certified to prescribe mifepristone, health care providers must submit a form attesting that they (1) can assess the duration of pregnancy accurately; (2) can diagnose ectopic pregnancies; (3) can provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and (4) have read and understood the prescribing information.

[121] Joint Stip. ¶ 57.

[122] *Id.* ¶ 41.

147. In 2016, the Agency's only documented rationale for maintaining ETASU A was that it "ensures that Mifeprex can only be dispensed by or under the direct supervision of a certified prescriber"[128]—a pure tautology.

148. In 2023, FDA reauthorized this ETASU because its "review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol."[129]

149. But FDA's rationale is premised on two wholly unsupported, purely speculative premises: (1) that clinicians providing pregnancy-related care would not already possess these fundamental abilities; and/or (2) that, in the absence of this ETASU, clinicians would prescribe mifepristone despite lacking appropriate qualifications.

150. FDA's explanation is medically unjustified for several reasons.

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[128] AR 0681.

[129] 2023 REMS Review, *supra* note 8, at 13–14; *accord, e.g.*, *id.* at 36; *accord* 2021 AAPLOG Pet. Denial, *supra* note 95, at 23.

151. *First*, numerous other mechanisms, including licensing requirements, ethical and professional obligations, and malpractice liability, exist to ensure that health care providers practice only to the extent of their training and abilities. An attestation of competency provides no greater assurance that a health care provider will not provide care outside of their scope of practice than do these existing legal requirements and ethical norms.

152. *Second*, there are countless other drugs that require careful patient screening to ensure safe use, yet are not subject to ETASU. Indeed, clinicians are not required to make a comparable attestation of their qualifications before prescribing Korlym—which is the *exact same product* as Mifeprex (mifepristone), in higher doses.

153. *Third*, fulfilling these criteria requires no specialized medical expertise. FDA has conceded that any provider who is not comfortable using patient medical history or a clinical examination to assess the duration and location of a pregnancy can obtain that information by ordering an ultrasound.

154. Similarly, any provider can arrange for emergency care by referring patients to an emergency room in the rare event that such care is needed. Indeed, as FDA acknowledged in a citizen petition denial issued on the *very same day* the Agency completed its December 2021 REMS Review concluding that the Prescriber

ETASU must be retained: "It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients."[130]

155. *Fourth*, as discussed *infra*, due to a number of factors, including the REMS, many patients are forced to travel outside their communities for abortion care. A patient who receives mifepristone from a REMS-certified provider outside her community and then initiates her medication abortion once she is back home generally will not (and should not) travel to seek in-person follow-up care from her REMS-certified prescriber; instead, she will receive any such follow-up care in her own community. The certification of the mifepristone prescriber thus has no bearing on the care the patient would receive in the unusual event of a complication.

156. *Finally*, reading and understanding the prescribing information for mifepristone is well within the scope of practice for any licensed prescriber.

iii. ETASU B: Pharmacy Certification

157. In order to dispense mifepristone, a pharmacy must become REMS-certified, which means agreeing to take on significant costs and burdens far beyond what is required for virtually every other prescription drug. These requirements include (but are not limited to) verifying that mifepristone prescriptions are written only by REMS-certified prescribers and storing prescriber certification information

[130] 2021 AAPLOG Pet. Denial, *supra* note 95, at 12.

in a manner that is both dynamic and confidential; tracking shipments of mifepristone by mail; engaging in two-way communications with the mifepristone prescriber regarding the timing of the medication's delivery; "reporting any patient deaths" (with no further clarification as to what this reporting entails); and being regularly audited for REMS compliance.

158. FDA concedes that the Pharmacy Certification ETASU is burdensome and will deter pharmacies from dispensing mifepristone: the Agency "acknowledge[d] that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS."[131] And FDA did not even account for any of the other burdens imposed by this ETASU beyond verifying prescriber certification, and their inevitable deterrence effect on pharmacy participation.

159. FDA justified adding this new ETASU based principally on its interaction with the prescriber certification requirement. FDA explained that "[w]ithout pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber."[132] The purpose of this ETASU is to "incorporate[] pharmacies into the REMS, ensure[] that pharmacies are aware of and

[131] 2023 REMS Review, *supra* note 8, at 14.

[132] *Id.* at 13.

agree to follow applicable REMS requirements, and ensure[] that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers."[133]

160. FDA nowhere addressed the fact that pharmacies had already been dispensing mifepristone for more than a year—from July 2020 until January 2021, and from April 2021 until December 2021—with *no* certification requirement and no increase in adverse events. Indeed, by January 3, 2023—when FDA completed its 2023 REMS Review, reauthorized the REMS, and for the first time imposed the Pharmacy Certification ETASU—pharmacies had been safely dispensing mifepristone without certification for well over two years.

c. Drugs That Pose Similar or Greater Risks Than Mifepristone Are Not Subject to Comparable Restrictions

161. The FDCA requires that, "to the extent practicable," ETASU "conform with elements to assure safe use for other drugs with similar, serious risks[.]" 21 U.S.C. § 355-1(f)(2)(D). But most other drugs that pose similar or greater risks than mifepristone are not subject to comparable restrictions.

162. As of November 2019, fewer than 3% of FDA-approved prescription drug products were subject to a REMS, 75% of which were opioids.

163. Many drugs that have higher safety risks than mifepristone are permitted to be marketed without restrictions comparable to the Mifeprex REMS.

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[133] *Id.*

164. For instance, Viagra is associated with death in up to 0.0026% of users, roughly 5 times the mifepristone-associated mortality rate.[136] And acetaminophen (Tylenol) toxicity is the most common cause of liver transplantation in the United States, and responsible for 56,000 emergency department visits, 2,600 hospitalizations, and 500 deaths per year in this country. Yet, neither Viagra nor Tylenol has a REMS.[137]

165. Similarly, as the *Chelius* Plaintiffs highlighted in their letter to FDA—and FDA nowhere addressed—many anticoagulant products, commonly known as "blood thinners," are associated with "serious and fatal bleeding," and, like mifepristone, carry warnings of that risk on their FDA-approved labels.[138] But unlike mifepristone, anticoagulants are a frequent cause of emergency room visits for documented hemorrhage.[139] Yet anticoagulants are available by prescription without

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[136] Lowe & Costabile, *supra* note 109, at 268-69.

[137] Suneil Agrawal & Babak Khazaeni, Acetaminophen Toxicity, Nat'l Library of Med. (Aug. 1, 2022), *available at* https://www.ncbi.nlm.nih.gov/books/NBK441917/#:~:text=It%20is%20responsible%20for%2056%2C000,is%20contained%20in%20combined%20products.

[138] *See, e.g.*, Coumadin® label, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf (containing boxed warning for, *inter alia*, "major or fatal bleeding"); Pradaxa® label, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022512s027lbl.pdf (warning of "serious and fatal bleeding"); Xarelto® label, *available at* https://www.xareltohcp.com/shared/product/xarelto/prescribing-information.pdf (same).

[139] Nadine Shehab, *et. al.*, *US Emergency Department Visits for Outpatient Adverse Drug Events*, 2013-2014, 316 J. Am. Med. Ass'n 2115-25 (2016) (17.6% of emergency room visits based on adverse drug events in 2013-2014 were related to anticoagulants, and of those, roughly 80% involved documented hemorrhage).

a REMS, whereas Mifeprex is not.

166. The *Chelius* Plaintiffs also highlighted in their letter to FDA that Jeuveau® is indicated for a purely cosmetic purpose among a healthy population—the "temporary improvement in the appearance of moderate to severe glabellar lines" (i.e., lines between one's eyebrows). It carries a black-box warning for "[s]wallowing and breathing difficulties" that "can be life threatening" if this botulinum toxin product spreads beyond the area of injection, and the labeling notes "there have been reports of death."[140] Yet FDA nowhere explained in its 2021 or 2023 REMS reviews why a REMS is necessary for mifepristone but not for Jeuveau.

167. In sum, the Mifepristone REMS and its ETASU are medically unjustified restrictions on abortion, as evidenced both by the drug's own record and by how FDA regulates other drugs with a safety profile comparable to or weaker than that of mifepristone.

168. These restrictions simply are not motivated by science.

D. The Impact of the Mifepristone REMS on Plaintiffs, Plaintiffs' Members, and Plaintiffs' Members' Patients

1. Harms Caused by the 2023 REMS

169. FDA's 2023 REMS reauthorization extends many of the same kinds of

[140] Jeuveau Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761085s000lbl.pdf (Feb. 2019).

burdens on patients and the health care delivery system that FDA's unique restrictions on mifepristone have imposed from the beginning.

170. ***First***, by continuing to classify mifepristone as among the tiny fraction of drugs for which REMS restrictions are necessary—on par with dangerous opioids causing "staggering" numbers of deaths each year—FDA's REMS reauthorization sends a false message about mifepristone's safety that complicates, delays, and derails efforts by health care providers to prescribe, research, and/or provide trainings on mifepristone.

171. For instance, clinicians seeking to begin prescribing mifepristone at their hospital or clinic have been required by health system leadership and/or decision-making committees to put together special presentations on mifepristone safety that are not required for other drugs with safety records comparable to mifepristone before the health care provider is permitted to prescribe it and/or the health system pharmacy is permitted to stock it. Such bureaucratic hurdles delay—and in some cases entirely prevent—health care providers in providing mifepristone to their patients, and would not arise if mifepristone were not subject to a REMS.

172. As another example, clinicians in doctoral programs have been unable to complete research and training projects relating to mifepristone because of institutional concerns and stigma expressly relating to mifepristone's classification as a REMS drug—e.g., requiring a doctoral student to seek Institutional Review

Board ("IRB") approval for a project that would not otherwise necessitate IRB approval, because it involves "a REMS drug."

173. ***Second,*** FDA's REMS reauthorization still means that a clinician seeking to prescribe mifepristone often must involve many other colleagues in their health system—such as administrators, nurses, and information technology staff—in the provision of mifepristone, which can delay or altogether derail their ability to provide this medication to their patients.

174. For instance, because FDA requires mifepristone prescribers to be specially certified, health systems may need to develop special systems to track and update clinicians' certifications. Because FDA requires mifepristone patients to sign a special counseling form, health care facilities that use electronic medical records must come up with a system for storing the signed Patient Agreement form in the patient's medical record, and health care facilities that wish to utilize telemedicine for mifepristone must implement HIPAA-compliant technology to allow for patients to remotely sign the Patient Agreement.

175. These and other logistical and technological burdens imposed by the REMS—layered on top of the broader deterrent effect of the REMS classification—frequently prevent patients from obtaining a mifepristone prescription from their primary health care provider.

176. ***Third***, by maintaining the Prescriber Certification ETASU, FDA continues to substantially reduce the pool of qualified health care providers willing to prescribe mifepristone because many clinicians are fearful that they will face anti-abortion violence and harassment if their registration as a mifepristone prescriber were ever exposed. FDA's own actions underscore the severity of this concern: the Agency redacted from the administrative record in this matter the names and offices of every one of its employees who has done any work relating to mifepristone. FDA explained that it feared that, "[i]n light of the violence and harassment surrounding the provision of abortion," releasing this information—*even subject to a protective order designed to ensure the confidentiality of that information*—"could expose those employees to threats, intimidation, harassment and/or violence."[142]

177. These fears are heightened now due to the growing criminalization and penalization of abortion care in many states across the country following *Dobbs v. Jackson Women's Health Org.*, with a particularly chilling effect on clinicians who hold medical licenses in multiple states, or medical residents who intend to eventually practice in a state with severe abortion restrictions. For instance, in recent years, several states have enacted laws allowing "bounty-hunter" vigilantes to drag into court anyone whom they suspect to have aided in the performance of an

[142] Joint Stip. of Facts. ¶ 47.

unlawful abortion, with no opportunity for the person sued to recover their litigation costs and fees even if they ultimately prevail. *See, e.g.*, Tex. Health & Safety Code § 171.208; Idaho Code Ann. § 18-8807.

178. ***Fourth***, by maintaining the Patient Agreement ETASU, FDA also retained a *de facto* in-person pill pick-up requirement for patients seeking mifepristone who do not themselves have the technology for a remote signature—e.g., no access to a smartphone or computer—or who seek mifepristone at a health center that does not have the technology in place to enable HIPAA-compliant remote signatures. As detailed *infra*, this is one of the many ways in which the 2023 REMS disproportionately harms low-income communities and communities of color.

179. ***Fifth***, the Patient Agreement ETASU *undermines* informed consent by requiring patients to review and sign a form containing fossilized science that may be inconsistent with their individual clinical circumstances. For example, the Patient Agreement states that the patient will take the misoprostol "24 to 48 hours" after taking the mifepristone. But some clinicians instruct patients to use an evidence-based protocol in which the misoprostol is taken simultaneously with mifepristone, or at another timeframe shorter than 24 hours, consistent with high-quality research and the patients' individual circumstances.[143] At best, the Patient Agreement

[143] *See, e.g.*, Nat'l Abortion Fed., 2022 Clinical Practice Guidelines 19 (2022), *available at* https://prochoice.org/wp-content/uploads/2022-CPGs.pdf.

duplicates counseling that mifepristone prescribers would already do, consistent with professional and ethical standards. More often, it complicates and confuses the counseling—particularly for patients with limited English proficiency who need translation services.

180. The Patient Agreement is often particularly confusing and distressing for patients using mifepristone for miscarriage care, who must attest that they are taking the medication "to end [their] pregnancy," even when this is false. Clinicians unwilling to require their patients undergoing miscarriages to sign a form containing knowingly false information about their medical condition and decision—or who work at a health care facility whose administration is concerned about the confusion or liability resulting from such a requirement—are unable to prescribe mifepristone to their patients experiencing early pregnancy loss at all.

181. ***Sixth***, by compelling patients using mifepristone to sign and take with them a form stating that they have had an abortion, FDA's REMS Reauthorization jeopardizes patients' privacy—because of the risk that the form will inadvertently be found by others with whom the patient might not otherwise disclose their pregnancy and/or abortion decision. Relatedly, by requiring that patients sign and take with them a form in which they attest that they have had an abortion, this ETASU increases the risk that patients will face anti-abortion violence and harassment (even if they actually used the mifepristone for miscarriage treatment).

182. ***Seventh***, the Pharmacy Certification ETASU imposes significant costs and burdens that deter pharmacies—especially smaller community pharmacies—from dispensing mifepristone, reducing patients' access to this medication. In order to comply with this ETASU, pharmacies seeking to dispense mifepristone must have the infrastructure and human and financial resources to, *inter alia*, develop a system to confidentially maintain prescriber certifications; verify that any prescription sent in for mifepristone comes from a certified prescriber; if the prescription does not come from a certified prescriber, either contact the prescriber to try to verify their certification or inform the patient that the prescription cannot be filled (in either case, delaying the patient's access); and train staff and prepare for special audits of their mifepristone REMS compliance procedures.

183. The Pharmacy Certification ETASU also necessitates that pharmacies commit to fill mifepristone prescriptions by mail using a carrier service that will ensure the medication is delivered within four calendar days, and if it appears the shipment may take more than four calendar days to arrive—e.g., due to a shipment delay or incomplete patient address—attempt to contact the prescriber to confirm "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 then maintain records documenting the prescriber's decision. By requiring that all shipments arrive within four calendar days except with documented

confirmation from the prescriber, the Pharmacy Certification ETASU necessitates that pharmacies use more expensive carrier services—and then either absorb those costs themselves (a further deterrent to become certified) or else pass those costs on to patients. This ETASU strips patients of the autonomy to choose a less expensive shipping option even if they know that, given the length of their pregnancy, receiving the medication in slightly more than 4 days would still be perfectly fine.

184. While some larger pharmacy chains or national mail-order pharmacies may be able to bear the financial and logistical burdens of the REMS requirements, mail-order delivery is not an appropriate option for many patients, such as those who are homeless or housing insecure or those living with an abusive partner or parent from whom they must keep their abortion decision private.

185. ***Eighth***, by prohibiting all but certified pharmacies to dispense mifepristone, FDA's REMS Reauthorization makes it practically impossible for many health care providers to know where to send the patient's prescription for fulfillment, particularly if the patient does not live in the prescriber's immediate area. There is no system to enable prescribers to know which pharmacies are certified. Without a REMS, clinicians can generally send in a prescription to the patient's preferred pharmacy, which will fill the medication if they have it in stock; request the medication from their pharmaceutical vendor; or else transfer the prescription to another pharmacy able to fill it. But the Pharmacy Certification ETASU replaces this

common and common-sense process with confusion and delay, and will necessitate that busy health care providers call around to multiple pharmacies or try to do research online in order to determine where to send the patient's prescription.

186. For the reasons described *supra* and others, the 2023 Mifepristone REMS Program unduly burdens patients' access to a safe and effective medication, compounding the profound abortion access issues that already exist in the United States—including in states where abortion remains legal after *Dobbs*. The REMS thus specifically harms "patients who [already] have difficulty accessing health care." 21 U.S.C. §355-1(f)(2)(C)(ii).

187. As the *Chelius* Plaintiffs highlighted in their 2021 submission to FDA, and FDA expressly ignored (*see supra* ¶¶ 103–06):

> A nationally representative sample of 8,000 abortion patients found that patients traveled, on average, 68 miles round-trip to receive an abortion. In a majority of states, at least 20% of reproductive-age women live more than 100 miles round-trip from the nearest abortion clinic. And while rural areas are particularly lacking, patients in urban areas also struggle. A 2018 study found that 27 major cities have no publicly advertised abortion provider within 100 miles.[144]

188. Like all restrictions on abortion, the burdens of the Mifepristone REMS Program are not borne equally. As the *Chelius* Plaintiffs explained, restrictions that

[144] Chelius Plaintiffs' Letter, *supra* note 10, at 5; *accord id.* at App. 089-122.

necessitate that patients travel farther in order to find a mifepristone provider, or make an extra medically unnecessary trip to a health center just to sign a form, can make it "incredibly difficult and in some cases impossible" for patients with unwanted pregnancies to access any abortion care at all.[145]

189. The REMS burdens are particularly harmful "[g]iven the mifepristone patient population."[146] As Plaintiffs explained:

> [I]n 2014 (the most recent year for which such data are available), 75 percent of abortion patients had incomes at or below the U.S. Official Poverty Measure. Sixty percent of abortion patients identify as people of color, including 53 percent of patients who identify as Black or Hispanic. And 60 percent of abortion patients have at least one child.[147]

By further reducing where abortion care is available in this country, the *Chelius* Plaintiffs told FDA, the REMS "imposes costs and burdens relating to transportation, childcare, and lost wages for missed work that many in this patient population simply cannot afford. Indeed, a robust body of research, spanning multiple states and decades, confirms that forcing patients to travel even slightly farther (e.g., 10 miles) delays or blocks patients from accessing desired abortions."[148]

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[145] *Id.*

[146] *Id.* at 5.

[147] *Id.* at 5–6.

[148] *Id.* at 6.

190. In addition to reducing the number of mifepristone prescribers, the 2023 REMS poses specific burdens for, *inter alia*, low-income populations (in which people of color are disproportionately represented because of structural racism), homeless populations (which disproportionately include LGBT people), people with limited English proficiency, and people living in abusive households. For example, without reliable and private access to a smartphone or computer with which to remotely sign the Patient Agreement form, patients are forced to make a wholly unnecessary trip to the health center when they could otherwise obtain their medication by mail or (potentially) at a local pharmacy. Likewise, people with housing insecurity who do not have a reliable mailing address must find and travel to a health center that stocks and dispenses mifepristone onsite when the burdens of the Pharmacy Certification ETASU prevent local retail pharmacies from stocking mifepristone. FDA failed to consider these and many other ways in which the mifepristone ETASU disproportionately harm patients that already face difficulties accessing healthcare.

2. Illustrative Harms to Plaintiffs and Plaintiffs' Members

191. Dr. Chelius is now able to prescribe mifepristone through a mail-order pharmacy, but he and his patients continue to experience harm as a result of the REMS. In particular, the REMS jeopardizes the privacy of Dr. Chelius's patients who need medication abortion care. Kauai Veterans, where Dr. Chelius works, is

located in Waimea, a small town of fewer than 2,000 people on the western side of Kauaʻi. Kauai Veterans employs nearly 500 people across the island, with the majority working at its Waimea hospital and clinic site; many employees, including Dr. Chelius, live nearby in the Waimea area. Most members of the community have a family member, friend, or neighbor employed at the hospital. Dr. Chelius recently provided a medication abortion to a patient who is a member of hospital staff. Generally, patient records are maintained through an electronic medical system, but the system does not have the capacity to store the Patient Agreement form—a unique form generated outside of the hospital system (*i.e.*, by FDA) that would need to be scanned in from a hard copy. In order to comply with the requirement in the Prescriber Agreement form that prescribers "ensure that the signed Patient Agreement Form is placed in the patient's medical record," Dr. Chelius would have to involve administrative staff in creating a hard copy file for his patient, thus revealing her private medical decision to her colleagues. In addition to causing direct harm to this patient and jeopardizing Dr. Chelius's relationship with someone who is both a patient and a colleague, Dr. Chelius is concerned about potential HIPAA implications of the Patient Agreement ETASU. In the insular community in which Dr. Chelius lives and works, there is a strong likelihood that similar privacy issues will arise again as a result of the REMS.

192. At this time, there are no brick-and-mortar pharmacies on Kaua‘i that are dispensing mifepristone. Several pharmacies on the island have indicated publicly or to Dr. Chelius or his colleagues that they would be willing to dispense mifepristone, but are uncertain whether they will be able to fulfill the requirements of the Pharmacy Certification ETASU and are still navigating those barriers. As previously detailed in this litigation, Dr. Chelius is unable to procure, stock, dispense, and bill for mifepristone onsite at his hospital because of opposition to abortion by colleagues who would need to be involved in those tasks, and because of the confidentiality concerns that doing so would pose in his tight-knit community. Establishing retail pharmacy access for mifepristone on the island is therefore critical for many of Dr. Chelius's patients for whom mail-order delivery is a poor option, for instance because they are homeless. Local access is particularly urgent for Dr. Chelius's patients who are nearing the gestational age limit for mifepristone because of both the logistics and cost of expedited delivery to the island of Kaua‘i—with overnight delivery from the contiguous United States being virtually impossible, and exacerbated by the time difference.

193. SFP and CAFP each has members experiencing harm(s) traceable to the REMS, including many or all of the harms detailed *supra*. For instance:

194. Sarah McNeil, MD, is a member of both SFP and CAFP and a family medicine doctor. Among other work, Dr. McNeil provides primary care, including

mifepristone for abortion and miscarriage, within a large county health system in northern California primarily serving a low-income patient population disproportionately comprising people of color. While there are more than 20 primary care offices located throughout the county—often hours apart from each other by car or bus—mifepristone is typically only prescribed at a single site within the county health system, and the REMS is impeding Dr. McNeil and her colleagues from expanding the provision of mifepristone to outlying clinics. She and her colleagues have already spent tens of hours over multiple years trying to navigate the administrative barriers imposed by the REMS, and developing technology to increase awareness of the REMS among clinicians across the health system and streamline their ability to make mifepristone available for abortion and miscarriage care. These efforts have yielded only limited success, and Dr. McNeil's work to surmount the REMS barriers is ongoing.

195. For instance, as a direct result of the Prescriber Certification ETASU, Dr. McNeil's health system requires that would-be mifepristone prescribers go through the added hurdle of obtaining internal privileges for mifepristone through their Medical Staff Office. To become credentialed, a clinician must submit an application that is then reviewed by the credentialing committee through a formal process occurring only once per month—delaying a clinician's ability to integrate mifepristone into their practice. Dr. McNeil's health system does not require OB-

GYN or Family Medicine doctors to obtain privileging before prescribing *any* other medication—only mifepristone.

196. As another example, the REMS creates an array of challenges for Dr. McNeil and her colleagues with respect to mifepristone dispensing. After countless meetings and emails with the numerous colleagues that must be involved in REMS compliance, Dr. McNeil's health system recently developed a process for its inpatient pharmacy to maintain records of whether a clinician is certified to prescribe mifepristone, and to dynamically update the system's electronic health records to reflect that information—a substantial and ongoing investment of human labor.

197. Even with this system in place, the Prescriber Certification ETASU is likely to still cause confusion and delays in patient care. Dr. McNeil's system has determined that, if a clinician unaware of the REMS requirements submits a mifepristone prescription to the health system's inpatient pharmacy without already being REMS-certified, someone at the inpatient pharmacy—which is also responsible for, *e.g.*, filling time-sensitive prescriptions for the hospital's intensive care unit—will have to send a copy of the certification form to that prescriber, who must then print, sign, and fax it back to the inpatient pharmacy before the prescriber can be considered temporarily privileged for mifepristone and the medication can be dispensed. Alternatively, if a clinician working at one of the few clinics in the county health system that stock mifepristone onsite writes a prescription for a patient

without having already been REMS-certified, the nurse responsible for dispensing medications would have to notify the prescriber that certification is required before it can be dispensed; the clinician would then have to coordinate with the inpatient pharmacy to complete their certification and fax it to the pharmacy; and the pharmacy would then have to get in touch with the nurse to give the green-light to dispense the mifepristone. Meanwhile, the patient either must wait at the clinic for this entire process to be completed in order to obtain their prescription, or else leave the clinic—for instance, because of work or family responsibilities—and then make another trip back at a later time to obtain the pill, with all of the burdens and costs of transportation, child care, and time off work that entails.

198. Dr. McNeil shares her story in her individual capacity and as an SFP and CAFP member, and not as a representative of any other institution.

199. Julie Jenkins, DNP, APRN, WHNP-BC, is a member of SFP and a nurse practitioner specializing in women's health who also holds a Doctor of Nursing Practice degree. The Doctor of Nursing Practice degree culminates in a final project intended to provide the doctoral candidate with an opportunity to publish and to gain other meaningful experience that will help position them for the academic job market. Dr. Jenkins intended to focus her project on developing and implementing a training on mifepristone for advanced practice registered nurses, the methodology and results of which she would then publish. However, Dr. Jenkins

faced repeated REMS-related hurdles in attempting to implement this straightforward project. For instance, while IRB approval would normally not be required for a project of this nature, Dr. Jenkins was advised by leadership at her academic institution to seek IRB approval—expressly because of mifepristone's REMS classification. Despite months of efforts to try to overcome these barriers, Dr. Jenkins was unable to complete the project at all, forfeiting an important professional opportunity. Indeed, Dr. Jenkins later had to explain in a job interview for an academic position why she did not complete a project during her doctoral program, and ultimately did not get that job.

200. Dr. Jenkins shares her story in her individual capacity and as an SFP member, and not as a representative of any other institution.

201. Angela Chen, MD, is a member of SFP and an OB-GYN practicing in a large university medical center in Los Angeles. Dr. Chen is a certified prescriber in the mifepristone REMS Program who prescribes mifepristone to patients seeking medication abortion and miscarriage care. But the Prescriber Certification ETASU poses significant burdens for Dr. Chen and her colleagues. Dr. Chen has colleagues within her institution and at the institution's satellite clinics who, although trained to provide medication abortion and miscarriage care with mifepristone, do not prescribe mifepristone because of the Prescriber Certification ETASU. These colleagues have informed Dr. Chen that they are not comfortable becoming certified

prescribers because of concerns about security and stigma if they were ever publicly identified as an abortion provider. Instead, they refer their patients who need mifepristone for medication abortion or miscarriage care to Dr. Chen and other certified prescribers in her practice. Similarly, OB-GYNs, family medicine physicians, internal medicine doctors, pediatricians, and other clinicians who practice in private settings and in community health centers in the Los Angeles area regularly refer patients to Dr. Chen and her colleagues for medication abortion and miscarriage care using mifepristone because they are unwilling or unable to become REMS-certified. These referrals occur nearly every week. Because of the frequency with which the referrals occur, and the time-sensitive medical care involved, these referrals impose burdens and logistical challenges for the certified prescribers as well as other institutional staff who have to work to try to squeeze these patients into already packed schedules.

202. The Patient Agreement ETASU also burdens Dr. Chen and her patients. Dr. Chen's institution uses an electronic medical record and e-signature system that could not accommodate the Patient Agreement form required under the REMS. As a result, they had to set up an entirely new system, separate from their existing system, to obtain e-signatures from the patients prescribed mifepristone. But even this does not fully solve the problem, because Dr. Chen and her colleagues have some patients who do not have smart phones or computers with which to sign the

form remotely. As a result, those patients must make an entirely unnecessary in-person trip to the health center just to sign the Patient Agreement form and pick up the pill, with all of the costs and logistics—including transportation, child care, and time off work—such travel entails. If not for the REMS, those patients could obtain their medication by mail (or at a local pharmacy) without having to make a trip to Dr. Chen's office.

203. The Patient Agreement ETASU has also imposed emotional harm on some of Dr. Chen's patients seeking care for miscarriage, because they are forced to sign a form that says they have decided to take mifepristone to end their pregnancy when they are, in reality, suffering the loss of a wanted pregnancy.

204. Dr. Chen shares her story in her individual capacity and as an SFP member, and not as a representative of any other institution.

205. Zeynep Uzumcu, MD, is a member of CAFP and a family medicine doctor specializing in obstetrics care. Among other work, she provides primary care at a safety net community health center serving a low-income population, disproportionately comprising people of color, in the northern central valley of California. In that capacity, Dr. Uzumcu regularly has patients present who are experiencing early pregnancy loss, and who request medication to complete the miscarriage. But Dr. Uzumcu is unable to provide her patients with the combined mifepristone-misoprostol regimen for early pregnancy loss because of the REMS.

For years, she and her colleagues have been attempting to make mifepristone available at their health center, but the clinic administration is deeply concerned about having to require miscarriage patients to sign a form stating that they are having an abortion. As a result, Dr. Uzumcu either offers patients the misoprostol-only regimen for miscarriage—while informing them that it is less effective than the combined regimen and thus they are more likely to require an additional in-office procedure if it fails—or else must refer them elsewhere for care. Both options have significant downsides: Dr. Uzumcu's patients in the midst of a miscarriage who opt to be referred elsewhere must make an extra visit to a health center, and typically cannot obtain an appointment (even with Dr. Uzumcu's help) for three to seven days. On the other hand, if patients opt for the misoprostol-only regimen and then have the treatment regimen fail, they generally must seek an in-office dilation and curettage procedure that they were hoping to avoid. Moreover, because Dr. Uzumcu's health center does not offer that service, such patients have to travel to another facility for the procedure, often with a multi-week delay before they can obtain an appointment. If not for the REMS, Dr. Uzumcu would be able to provide her patients with the preferred treatment regimen for medical management of miscarriage.

206. Dr. Uzumcu shares her story in her individual capacity and as a CAFP member, and not as a representative of any other institution.

207. Panna Lossy, MD, is a member of CAFP and a family medicine doctor; she also currently serves as the North Bay Chapter President for CAFP and as an alternate delegate to the CAFP board of directors. Dr. Lossy previously ran an early pregnancy options clinic within a full-spectrum primary care practice in California, where she was a certified mifepristone prescriber. She has retired from that role, but is still regularly contacted by doctors who want to integrate mifepristone into their practices and seek Dr. Lossy's help understanding and navigating the REMS barriers—including numerous such requests for help in the two months since FDA's 2023 REMS reauthorization. Doctors frequently seek out Dr. Lossy, for instance, to discuss their fears about being on an abortion provider "list," or to strategize about how they can try to reduce the burdens of REMS compliance on other departments within their health care system. Unfortunately, while Dr. Lossy can tell these colleagues that there are measures in place to try to ensure the confidentiality of mifepristone prescriber certifications, it is impossible for her to reassure them that they would not face anti-abortion violence or harassment if their certification as a mifepristone prescriber were to be leaked—especially now, post *Dobbs*. Ultimately, even with Dr. Lossy's help, the REMS often delays or deters clinicians with whom she consults from becoming certified mifepristone prescribers.

208. While Dr. Lossy is motivated to provide this support because of her commitment to expanding safe and equitable access to reproductive health care,

these conversations require time that she would otherwise spend on paid work or time with her family. Dr. Lossy does not have comparable conversations with respect to any other drug or health care service, and if FDA regulated mifepristone like other equally safe prescription drugs, these REMS-related burdens on Dr. Lossy would be eliminated.

209. Dr. Lossy shares her story in an individual capacity and as a member of CAFP and SFP, not on behalf of any other institution.

210. Additionally, SFP and CAFP each must divert resources from other organizational priorities to try to mitigate the burdens of the mifepristone REMS.

211. For instance, separate and apart from this litigation, SFP regularly participates in meetings and consults with members regarding the impact of the REMS and how to mitigate the burdens of those restrictions, and is in the process of developing guidance about seeking IRB approval for studies relating to abortion and contraception that may include a component about navigating the mifepristone REMS. These efforts require staff time and resources that SFP would otherwise spend on other clinical and policy matters relating to abortion and contraception.

212. Similarly, separate and apart from this litigation, CAFP regularly participates in meetings and consults with members regarding the impact of the mifepristone REMS and how to mitigate the burdens of those restrictions. CAFP has also engaged in specific efforts to educate its members about compliance with the

REMS, for instance through a webinar. These efforts require staff time and resources that CAFP would otherwise spend on advocacy, clinical education, professional development, and other efforts to support its family physician members.

CLAIMS FOR RELIEF

COUNT I

(Equal Protection)

213. The allegations of paragraphs 1 through 212 are incorporated as though fully set forth herein.

214. The Mifepristone REMS Program violates Plaintiffs', Plaintiffs' members', and Plaintiffs' members' patients' right to equal protection of the laws under the Fifth Amendment to the United States Constitution by treating Plaintiffs, Plaintiffs' members, and Plaintiffs' members' patients differently from other similarly situated parties without a sufficient state interest.

COUNT II

(Administrative Procedure Act: Contrary to Constitutional Right)

215. The allegations of paragraphs 1 through 212 are incorporated as though fully set forth herein.

216. FDA's 2023 reauthorization of the mifepristone REMS and other agency action and inaction described herein constituted final agency action for

which Plaintiffs have no other adequate remedy within the meaning of 5 U.S.C. § 704.

217. FDA's 2023 reauthorization of the mifepristone REMS and other agency action and inaction described herein is contrary to Plaintiffs', Plaintiffs' members', and Plaintiffs' members' patients' constitutional rights, including their rights under the Fifth Amendment to the U.S. Constitution, in violation of 5 U.S.C. § 706(2)(B).

COUNT III

(Administrative Procedure Act: In Excess of Statutory Authority)

218. The allegations of paragraphs 1 through 212 are incorporated as though fully set forth herein.

219. FDA's 2023 reauthorization of the mifepristone REMS and other agency action and inaction described herein constituted final agency action for which Plaintiffs have no other adequate remedy within the meaning of 5 U.S.C. § 704.

220. FDA's 2023 reauthorization of the mifepristone REMS and other agency action and inaction described herein is in excess of the Agency's statutory authority under the FDCA in violation of 5 U.S.C. § 706(2)(C).

COUNT IV

**(Administrative Procedure Act:
Arbitrary, Capricious, Abuse of Discretion, and Contrary to Law)**

221. The allegations of paragraphs 1 through 212 are incorporated as though fully set forth herein.

222. FDA's 2023 reauthorization of the mifepristone REMS and other agency action and inaction described herein constituted final agency action for which Plaintiffs have no other adequate remedy within the meaning of 5 U.S.C. § 704.

223. FDA's 2023 reauthorization of the mifepristone REMS was not based on any reasoned decision or rational basis, and therefore was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

224. FDA's 2023 reauthorization of the mifepristone REMS treated similarly situated entities differently without adequate justification, and therefore was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

225. FDA's 2023 reauthorization of the mifepristone REMS violated the Agency's governing statute and therefore is not in accordance with law in violation of 5 U.S.C. § 706(2)(A).

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that the Court enter judgment in their favor and:

1) Declare, pursuant to 28 U.S.C. § 2201, that the mifepristone REMS in its entirety, as set forth above, violates the Fifth Amendment of the United States Constitution; and/or
2) Declare, pursuant to 28 U.S.C. § 2201, that certain components of the mifepristone REMS violate the Fifth Amendment of the United States Constitution:
    a. ETASU A (Prescriber Certification); and/or
    b. ETASU B (Pharmacy Certification); and/or
    c. ETASU D (Patient Agreement Form); and/or
    d. Implementation System; and/or
    e. Timetable for Assessments; and/or
3) Declare, pursuant to 28 U.S.C. § 2201, that the mifepristone REMS in its entirety, as set forth above, violates the Administrative Procedure Act; and/or
4) Declare, pursuant to 28 U.S.C. § 2201, that certain components of the mifepristone REMS violate the Administrative Procedure Act:
    a. ETASU A (Prescriber Certification); and/or
    b. ETASU B (Pharmacy Certification); and/or

c. ETASU D (Patient Agreement Form); and/or

d. Implementation System; and/or

e. Timetable for Assessments; and

5) Enter an injunction prohibiting Defendants, their employees, agents, and successors in office, from requiring a REMS for Mifeprex (mifepristone), NDA 020687, mifepristone (ANDA 091178), or any future ANDA associated with these applications; and/or

6) Remand to FDA with instructions to remove the Mifepristone REMS Program while maintaining the approvals of Mifeprex (mifepristone), NDA 020687, and mifepristone (ANDA 091178); and

7) Award to Plaintiffs costs, expenses, and attorneys' fees pursuant to 28 U.S.C. § 2412; and

8) Award such other, further, and different relief as the Court deems just and proper.

DATED: Honolulu, Hawai‘i, March 30, 2023.

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Suppl. Ex. A

U.S. Food & Drug Admin., REMS Review Memorandum (Jan. 3, 2023)

[redacted] and [redacted]

Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 091178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequences 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022 (sequences 24 and 92 respectively), December 9, 2022 (sequences 25 and 93 respectively) and December 16, 2022 (sequences 26 and 95 respectively). This supplement is on a 180-Day clock.
Targeted Action Date	December 19, 2022
[redacted] #	2022-1169
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	January 3, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS
Name of Sponsor	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

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EXECUTIVE SUMMARY

This is a review of the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178. The Sponsors submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, and amended their submissions on October 19, 2022 (Danco), October 20, 2022 (GBP), November 30, 2022 (both), December 9, 2022 (both) and December 16, 2022 (both).

The Mifepristone REMS Program was originally approved on April 11, 2019, to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021.[a] The Mifepristone REMS Program consists of elements to assure safe use (ETASU) A, C and D, an implementation system, and a timetable for submission of assessments of the REMS.

The Sponsors submitted the proposed modification to the REMS in response to the Agency's REMS Modification Notification letters dated December 16, 2021, which required removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") and the addition of certification of pharmacies that dispense the drug.

In addition, the following were addressed during the course of the review:

- revisions to the REMS goal to align with the updated REMS requirements.
- replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms*, *Patient Agreement Form*, and *Pharmacy Agreement Forms*).

The review team finds the proposed modification to the Mifepristone REMS Program last submitted on December 16, 2022, to be acceptable and recommends approval of the REMS modification. The proposed REMS modification includes changes to the REMS goal, additional REMS requirements for prescribers to incorporate dispensing from certified pharmacies and new REMS requirements for pharmacy certification.

The proposed goal of the modified REMS for mifepristone 200 mg 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.

[a] The May 14, 2021 REMS modification approved the inclusion of gender neutral language in the Patient Agreement Form as well as corresponding minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

The timetable for submission of assessments of the REMS was modified to one year from the date of the approval of the modified REMS and annually thereafter. The assessment plan was revised to align with the changes to the REMS and capture additional metrics for drug utilization and REMS operations.

The modified REMS includes ETASU A, B and D, an implementation system, and a timetable for submission of assessments of the REMS. Mifepristone will no longer be required to be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement" for brevity) and will be able to be dispensed from certified pharmacies.

1. Introduction

This review evaluates the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Sponsors initially submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, in response to the Agency's REMS Modification Notification letters issued on December 16, 2021, to Danco and GBP, requiring the following modification to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

Per the Agency's December 16, 2021, REMS Modification Notification letters, the proposed REMS was required to include the following ETASU to mitigate the risk of serious complications associated with mifepristone, including at least the following:

- healthcare providers have particular experience or training, or are specially certified
- pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- the drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS was also required to include an implementation system and timetable for submission of assessments.

2. Background

2.1. Product Information and REMS Information

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

the risk of serious complications associated with mifepristone when used for medical abortion.[c] Mifeprex was deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and the Mifeprex REMS was approved on June 8, 2011.

On March 29, 2016, FDA approved an efficacy supplement for Mifeprex, which included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol, as well as a modification of the gestational age up to which Mifeprex has been shown to be safe and effective and a modification to the process for follow-up after administration of the drug. FDA also approved modification to the Mifeprex REMS that reflected the changes approved in the efficacy supplement.[1-5] On April 11, 2019, FDA approved ANDA 091178 and the Mifepristone REMS Program.[6-7] The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 091178. The goal of the approved Mifepristone REMS Program 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 (under ETASU A).
b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber (under ETASU C).
c) Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

The Mifepristone REMS Program was last modified and approved in 2021 to revise the *Patient Agreement Form* to include gender-neutral language; however, the goal of the Mifepristone REMS Program has not changed since the initial approval in 2019.

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and agree to follow the guidelines for use of mifepristone. Under ETASU C, in the Mifepristone REMS Program as approved prior to today's action, mifepristone was required to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The approved Mifepristone REMS Program includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public health emergency (PHE) regarding the in-person dispensing requirement in the Mifepristone REMS Program. Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020, to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[8]

[c] Mifepristone is also approved in approximately 80 other countries. https://gynuity.org/assets/resources/biblio_ref_lst_mife_en.pdf

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 04/11/2019: Approval of the Mifepristone REMS Program, a single, shared system REMS that includes NDA 020687 and ANDA 091178.
- 04/12/2021: The Agency issued a General Advice letter to both the NDA and ANDA Applicants, explaining that FDA intended to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.
- 05/07/2021: The Agency stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with section 505-1 of the FD&C Act.
- 12/16/2021: The Agency completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification.[9]
- 12/16/2021: REMS Modification Notification letters were sent to both Sponsors stating that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare system of complying with the REMS and ensure that the benefits of the drug outweigh the risks.
- 04/08/2022: Final written responses to a Type A meeting request were provided to Danco, the point of contact for the Mifepristone REMS Program. The questions pertained to the 12/16/2021 REMS Modification Notification letter requirements.
- 04/13/2022: The Sponsors requested an extension to 6/30/2022, to submit a proposed REMS modification in response to the Agency's 12/16/2021 REMS Modification Notification letters.
- 04/15/2022: The Agency granted the Sponsors' request for an extension to submit a proposed REMS modification and conveyed that the modification must be submitted no later than 06/30/2022.[10]
- 06/22/2022: Danco and GBP submitted a proposed REMS modification to their respective applications in response to the 12/16/2021 REMS Modification Notification letters.
- 07/22/2022: An Information Request was sent to the Sponsors requesting clarification of the proposed prescriber and dispenser requirements and additional rationale to support their proposal.
- 08/26/2022: Sponsors submitted responses to 07/22/2022 Information Request.
- 09/19/2022: Teleconference was held between Agency and Sponsors where the Agency communicated the REMS requirements that are necessary to support the addition of pharmacy

certification. The Agency proposed focusing on the pharmacy settings where a closed system[d] REMS could be implemented using the existing email and facsimile based system, (b) (4) , as the best strategy for an approvable modification by the goal date.

- 09/22/2022: An Information Request was sent to Sponsors requesting confirmation that the Sponsors agree with the pharmacy distribution approach outlined in the 09/19/2022 teleconference so that the Agency's feedback could be appropriately tailored.
- 09/23/2022: The Sponsors confirmed via email that they were willing to pursue (b) (4) , as discussed in the 09/19/2022 teleconference. The Sponsors also requested a teleconference to discuss the current modification (b) (4) .
- 09/27/2022: Comments from the 09/19/2022 teleconference sent to Sponsors with additional comments and requests regarding what will be necessary for pharmacy certification.
- 09/29/2022: An Information request was sent to the Sponsors asking for agenda items, questions, and a request to walk through their proposed system for pharmacy certification, including dispensing through mail-order or specialty pharmacies, at the 10/06/2022 scheduled teleconference.
- 10/04/2022: Sponsors emailed that they will focus the 10/06/2022 teleconference on the 09/27/2022 Agency comments and their mail order and specialty pharmacy distribution model.
- 10/06/2022: Teleconference was held between Agency and Sponsors where Sponsors outlined their proposal for pharmacy certification, including dispensing through mail order and specialty pharmacies, as well as their concerns with certain requirements and general timelines.
- 10/19/2022: Danco submitted a REMS amendment to their pending sNDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/20/2022: GBP submitted a REMS amendment to their pending sANDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/25/2022: Teleconference was held between Agency and Sponsors to discuss the *Patient Agreement Form* and timing related to shipping a mifepristone prescription from a certified pharmacy to the patient.
- 11/23/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document, submitted on 10/19/2022 (Danco) and 10/20/2022 (GBP).
- 11/30/2022: Danco and GBP submitted REMS amendments, which included the REMS Document, to their respective pending supplemental applications.
- 12/01/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document.
- 12/05/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document submitted on 11/30/2022 and discussed at the teleconference on 12/01/2022, and REMS materials submitted to their applications on 10/19/2022 and 10/20/2022.

[d] "Closed system" in this case refers to a system where prescribers, pharmacies, and distributors are certified or authorized in the REMS and the certification of the stakeholder must be verified prior to distribution or dispensing, as per the REMS.

- 12/07/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document and REMS materials the Agency sent to the Sponsors on 12/05/22.
- 12/08/2022: Danco and GBP submitted REMS amendments, including the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form, Patient Agreement Form* and REMS Supporting Document, to their respective pending applications.
- 12/09/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS assessment plan.
- 12/14/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form*, and REMS Supporting Document.
- 12/15/2022: Two teleconferences were held between Agency and Sponsors to discuss the proposed REMS Document and REMS materials the Agency sent to the Sponsors on 12/14/22.
- 12/16/2022: Sponsors submitted a REMS amendment to their respective applications.

3. Review of Proposed REMS Modification

(b) (6) has discussed the Sponsors' proposed modification with the review team, which includes members of the (b) (6) and the (b) (6) ; hereafter referred to as the review team. This review includes their input and concurrence with the analysis and proposed changes to the Mifepristone REMS Program.

3.1. REMS Goal

The Sponsors proposed modification to the goal for the Mifepristone REMS Program to add that mifepristone can also be dispensed from certified pharmacies on prescriptions issued by certified prescribers. The proposed REMS goal is:

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.

Reviewer Comment: *We agree with the Sponsors' proposal.*

3.2. REMS Document

The proposed REMS Document is not in the format as outlined in the 2017 Draft Guidance for Industry, Format and Content of a REMS Document.[11]

Reviewer Comment: *To avoid the misperception that this REMS modification is making major changes to the REMS document that go beyond our December 16, 2021, determination that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification, CDER staff and management discussed whether to change the format of the REMS document to that described in the 2017 draft guidance.*[11] *After internal discussion, CDER staff and management aligned not to transition the REMS document at this time to the format described in the 2017 draft guidance.*

3.3. REMS Requirements

3.3.1. Addition and Removal of ETASU

The December 16, 2021, REMS Modification Notification letters specified that the ETASU must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure the benefits of the drug outweigh the risks by:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices and hospitals (i.e., the "in-person dispensing requirement"), and;
- Adding a requirement that pharmacies that dispense the drug be specially certified.

The Sponsors proposed changes to the REMS as reflected in the subsections below.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Prescriber Requirements

Consistent with the approved Mifepristone REMS Program prescribers must be specially certified. To become specially certified to prescribe mifepristone, healthcare providers who prescribe must review the Prescribing Information for mifepristone and complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet certain qualifications and will follow the guidelines for use of mifepristone. The guidelines for use include ensuring i) that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained; ii) that the healthcare provider (HCP) and the patient sign the *Patient Agreement Form*, iii) the patient receives a copy of the *Patient Agreement Form* and Medication Guide, iv) the *Patient Agreement Form* is placed in the patient's medical record; v) that any patient 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. The language on the guidelines for use was revised from the Mifepristone REMS Program approved in 2021 to clarify that, if the certified prescriber supervises the dispensing of mifepristone, they must ensure the guidelines for use of mifepristone are followed by those under their supervision. This clarification reflects the ongoing implementation of the approved Mifepristone REMS Program. For example, consistent with the approved REMS, the *Patient Agreement Form* does not require the certified prescriber's signature, but rather the signature of the healthcare provider counseling the patient on the risks of mifepristone. Additional changes were made globally to provide consistency and clarity of the requirements for certified prescribers and healthcare providers who complete tasks under the supervision of certified prescribers.

A certified prescriber may submit the *Prescriber Agreement Form* to an authorized distributor if the certified prescriber wishes to dispense or supervise the dispensing of mifepristone; this is consistent with the current requirements of the Mifepristone REMS Program. Additional requirements were

added to incorporate mifepristone dispensing by a certified pharmacy. If a healthcare provider wishes to prescribe mifepristone by sending a prescription to a certified pharmacy for dispensing, the healthcare provider must become certified by providing the pharmacy a *Prescriber Agreement Form* signed by the provider. A certified prescriber must also assess the appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy.

The NDC and lot number of the dispensed drug will be recorded in the patient's record when mifepristone is dispensed by or under the supervision of a certified prescriber, replacing the requirement that serial numbers from each package of mifepristone be recorded in the patient's record. If prescribers become aware of the death of a patient for whom the mifepristone was dispensed from a certified pharmacy, the prescribers will be required to obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy.

The following materials support prescriber requirements:

- *Prescriber Agreement Form* for Danco Laboratories, LLC
- *Prescriber Agreement Form* for GenBioPro, Inc.
- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

Although certain activities (review of the Patient Agreement Form with patients and answering any questions about treatment, signing, providing a copy to the patient and retaining the Patient Agreement Form, providing a copy of the Medication Guide, and ensuring any deaths are reported to the Mifepristone Sponsor, recording the NDC and lot number from drug dispensed from the certified prescriber or those under their supervision) may be conducted by healthcare providers under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. We agree with the additional language to further clarify that the certified prescriber must ensure the guidelines for use of mifepristone are followed.

As proposed, certified prescribers may either, 1) continue to submit the Prescriber Agreement Form to an authorized distributor if the certified prescriber is dispensing or supervising the dispensing of the drug (as already required in the REMS), or 2) if the drug will be dispensed from a certified pharmacy, submit the Prescriber Agreement Form to the certified pharmacy that will dispense the drug (as proposed in the modification). Regarding #2, the pharmacy can only fill prescriptions written by a certified prescriber.

Based on our review of the proposed changes, the review team finds it acceptable for prescribers to submit their Prescriber Agreement Form directly to the certified pharmacy. Although certified prescribers still have the option of in-person dispensing of the drug, not all prescribers may want to stock mifepristone. Typically due to the number of drugs that are available and the expense associated with stocking prescription medications intended for outpatient use, most prescribers do not stock many medications, if they stock medications at all.

The proposal to submit a Prescriber Agreement Form to a certified pharmacy provides another option for dispensing mifepristone. The burden of providing the Prescriber Agreement Form prior to or when the prescription is provided to a certified pharmacy does not create unreasonable burden for prescribers. The burden of prescriber certification has been minimized to the extent possible. The Prescriber Agreement Form is designed to require minimal time to complete and requires that the prescriber submit it to the authorized distributor once, and if the prescriber chooses to use a certified pharmacy to dispense mifepristone, they will need to submit the form to the certified pharmacy.

There is an additional requirement added for certified pharmacies and certified prescribers in the event that a patient will not receive their medication from the certified pharmacy within four calendar days of the pharmacy's receipt of the prescription (for example, if the medication is not in stock). In this circumstance, the pharmacy will be required to contact the certified prescriber to make them aware of the delay and will be required to obtain from the prescriber confirmation that it is appropriate to dispense mifepristone to the patient even though they will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy. This confirmation is intended to ensure timeliness of delivery in light of the labeled indication and gestational age. Additional details and rationale on the pharmacy requirements to dispense and ship drug in a timely manner are described in section 3.3.2.3.

If a certified prescriber becomes aware of a patient death that occurs subsequent to the use of mifepristone dispensed from a pharmacy, the certified prescriber must obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy. This information will be reported to the appropriate Mifepristone Sponsor in the same manner prescribers have done previously. This additional requirement to obtain the NDC and lot number from the pharmacy is needed to ensure consistent adverse event reporting when mifepristone is dispensed from a certified pharmacy.

Prescriber Agreement Form

The Sponsors' proposed changes to the *Prescriber Agreement Form* aligned with those described above. The proposed *Prescriber Agreement Form* explains the two methods of certification which are: 1) submitting the form to the authorized distributor and 2) submitting the form to the dispensing certified pharmacy. Further clarification was added that 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. The statement that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program was also added. The following statement was added to the form: "I understand that the pharmacy may dispense mifepristone made by a different manufacturer than that stated on the Prescriber Agreement Form." The account set up information was removed and replaced with prescriber information response fields.

***Reviewer Comment**: We agree with the Sponsors' proposal. Changes in the above prescriber requirements were incorporated in the Prescriber Agreement Form.*

3.3.2.2. Patient Requirements

The *Patient Agreement Form* was updated to clarify that the signatures may be written or electronic, to reorganize the risk information about ectopic pregnancy, and to remove the statement that the Medication Guide will be taken to an emergency room or provided to a healthcare provider who did not prescribe mifepristone so that it is known that the patient had a medical abortion with mifepristone.

The following materials support patient requirements:

- *Patient Agreement Form*

***Reviewer Comment:** We agree with the Sponsors' proposal.*

The Patient Agreement Form continues to be an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the

patient, to provide the patient with the Patient Agreement Form, and to have the healthcare provider and patient sign the Patient Agreement Form, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The form is signed by the patient and the provider and placed in the patient's medical record, and a copy is provided to the patient, to document the patient's acknowledgment of receiving the information from the prescriber. The Agency agrees that the further clarification that signatures can be written or electronic is appropriate for the continued use of the form.

The reference to ectopic pregnancy has been reorganized in the document since it is not a risk of the drug. The signs and symptoms of an untreated ectopic pregnancy that may persist after mifepristone use have been clarified in the section of the form that explains the signs and symptoms of potential problems that may occur after mifepristone use.

The review team agrees with removing the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion. Although this statement has been in the Medication Guide for a number of years, upon further consideration, the Agency has concluded that patients seeking emergency medical care are not likely to carry a Medication Guide with them, the Medication Guide is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

3.3.2.3. Pharmacy Requirements

The Sponsors proposed that certified pharmacies, in addition to certified prescribers and HCPs under the supervision of certified prescribers, can dispense mifepristone. In order for a pharmacy to become certified, the pharmacy 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. The Authorized Representative must certify that they have read and understood the Prescribing Information for mifepristone. Each location of the pharmacy must be able to receive *Prescriber Agreement Forms* by email and fax and be able to ship mifepristone using a shipping service that provides tracking information.

Additionally, each dispensing pharmacy location must put processes and procedures in place to fulfill the REMS requirements. Certified pharmacies must verify prescriber certification by confirming they have obtained a copy of the prescriber's signed *Prescriber Agreement Form* before dispensing. Certified pharmacies must dispense mifepristone such that it is received by the patient within four days from the day of prescription receipt by the pharmacy. If the pharmacy will not be able to deliver mifepristone to the patient within four days of receipt of the prescription, the pharmacy must contact the prescriber to confirm the appropriateness of dispensing mifepristone and document the certified prescriber's decision. The pharmacy must also record the NDC and lot number from each package of mifepristone dispensed in the patient's record, track and verify receipt of each shipment of mifepristone, dispense mifepristone in its original package, and only distribute, transfer, loan, or sell mifepristone to certified prescribers or between locations of the certified pharmacy. The pharmacy must also report any patient deaths to the prescriber, including the NDC and lot number from the package dispensed to the patient, and remind the prescriber of their obligation under the REMS to report patient deaths to the Sponsor that supplied the mifepristone; the certified pharmacy also must notify the Sponsor that supplied the mifepristone that the pharmacy submitted a report of a patient death to the prescriber and include the name and contact information for the prescriber as well as the NDC and lot number of the dispensed

product. Record-keeping requirements of the pharmacy include records of *Prescriber Agreement Forms*, mifepristone dispensing and shipping, and all processes and procedures and compliance with those processes and procedures. Pharmacies must train all relevant staff and participate in compliance audits. Pharmacies must also maintain the identity of patients and providers as confidential, including limiting access to patient and provider 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. The requirement that mifepristone not be dispensed from retail pharmacies was removed.

The following materials support pharmacy requirements:

- *Pharmacy Agreement Form* for Danco Laboratories, LLC
- *Pharmacy Agreement Form* for GenBioPro, Inc.

Reviewer Comment: *We agree with the Sponsors' proposal. The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, mifepristone can be dispensed from a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that the prescriber is certified prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the Patient Agreement Form is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review and our consideration of the distribution model implemented by the Sponsors during the periods when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients.*

The requirement to maintain confidentiality, including limiting access to patient and provider identity only to those personnel necessary for dispensing under the Mifepristone REMS Program or as necessary for payment and/or insurance purposes, is included to avoid unduly burdening patient access.

The Sponsors proposed inclusion of this requirement because of concerns that patients may be reluctant or unwilling to seek to obtain mifepristone from pharmacies if they are concerned that confidentiality of their medical information could be compromised, potentially exposing them to intimidation, threats, or acts of violence by individuals opposed to the use of mifepristone for medical abortion.[e] *Further, unwillingness on the part of prescribers to participate in the Mifepristone REMS Program on the basis of*

[e] See e.g., *2020 Violence and Disruption Statistics,* National Abortion Federation (Dec. 16, 2021), https://prochoice.org/national-abortion-federation-releases-2020-violence-disruption-statistics/; Amanda Musa, CNN, *Wyoming Authorities Search for a Suspect Believed to Have Set an Abortion Clinic on Fire*, CNN WIRE (June 10, 2022), https://abc17news.com/news/2022/06/10/wyoming-authorities-search-for-a-suspect-believed-to-have-set-an-abortion-clinic-on-fire/.

similar confidentiality concerns may unduly burden patient access by limiting the number of prescribers who are willing to send prescriptions to certified pharmacies. Addition of this requirement protects patient access by requiring the pharmacy to put processes and procedures in place to limit access to confidential information to only those individuals who are essential for dispensing mifepristone under the Mifepristone REMS Program or as necessary for payment or insurance purposes. Inclusion of this requirement for certified pharmacies is consistent with the requirement in the current Mifepristone REMS Program, that distributors maintain secure and confidential records.

Reference to mifepristone not being available in retail pharmacies was removed from the REMS. There is no single definition of the term "retail pharmacy" and therefore the scope of the exclusion in the REMS was not well defined. Including a restriction in the Mifepristone REMS Program that retail pharmacies cannot participate in the REMS may unintentionally prohibit the participation of mail order and specialty pharmacies that could, under one or more definitions, also be considered a "retail pharmacy."

After reconsideration of the term, "retail," the Agency concluded that a more appropriate approach was to articulate the specific requirements that would be necessary for pharmacy certification. As modified, the REMS will not preclude the participation of any pharmacy that meets the certification requirements. However, we acknowledge that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS. The REMS requires that pharmacies dispense mifepristone only after verifying that the prescriber is certified. The REMS further requires that pharmacies be able to receive the Prescriber Agreement Forms by email and fax. (b) (4)

The pharmacy certification requirements include that the drug reach patients within four days of the certified pharmacy receiving the prescription. During the course of the review, the review team concluded that requiring medication delivery to the patient within four days of the pharmacy's receipt of a prescription is acceptable based on the labeled indication and literature,[13] while taking into account practical shipping considerations (e.g., shipping over weekends and holidays). For patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription, the pharmacy must notify the certified prescriber and the certified prescriber must determine if it is still appropriate for the certified pharmacy to dispense the drug. The pharmacy must document the certified prescriber's decision. A prescriber's confirmation that it is appropriate to dispense mifepristone when it will not be delivered to the patient within the allotted four days is intended to ensure timeliness of delivery in light of the labeled indication and gestational age.

Pharmacy Agreement Form

The proposed *Pharmacy Agreement Form* is a new form and is the means by which a pharmacy becomes certified to dispense mifepristone. The form, which is submitted by an authorized representative on behalf of a pharmacy seeking certification, outlines all requirements proposed above. Clarification is included in the form that 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. Any new authorized representative must complete and submit the *Pharmacy Agreement Form*. Spaces for specific authorized representative information and pharmacy name and address are included. The completed form can be submitted by email or fax to the authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The Pharmacy Agreement Form aligns with the pharmacy requirements discussed above.*

3.3.2.4. Distributor Requirements

The Sponsors proposed that the distributors' processes and procedures in the approved Mifepristone REMS Program be updated to ensure that mifepristone is only shipped to clinics, medical offices and hospitals identified by certified prescribers and to certified pharmacies. Distributors will continue to complete the certification process for any *Prescriber Agreement Forms* they receive and also will complete the certification process for pharmacies upon receipt of a *Pharmacy Agreement Form*, including notifying pharmacies when they become certified. FDA was removed as a potential auditor for distributors.

Reviewer Comment: *We agree with the Sponsors' proposal. At this time, FDA does not audit distributors directly, it carries out inspections of Sponsors to monitor industry compliance with REMS requirements.*

3.3.3. REMS Sponsor Requirements

3.3.3.1. Sponsor Requirements to Support Prescriber Certification

The Sponsors proposed additions to this section of the REMS document, including that Sponsors will ensure prescribers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy, and that Sponsors will ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date. Sponsors will also 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, or (2) within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The requirement to confirm that the locations associated with the certified prescriber are current is parallel to the pharmacy requirement that the authorized representative's contact information is up to date. In determining the pharmacy requirement, which is necessary to ensure program compliance and is consistent with other approved REMS that include pharmacy certification, the Agency also concluded that a parallel requirement for certified prescribers should be added.*

With respect to recertification, it is important that active certified prescribers are informed of and agree to new REMS requirements to ensure the continued safe use of mifepristone. There is minimal burden to recertification and the timelines allow sufficient time to accomplish recertification.

3.3.3.2. Sponsor Requirements to Support Pharmacy Certification

The Sponsors proposed the addition of Sponsor requirements to support pharmacy certification and compliance, including ensuring that pharmacies are certified in accordance with the requirements in the Mifepristone REMS Program, de-certifying pharmacies that do not maintain compliance with the certification requirements, and ensuring that pharmacy certification can be completed by email and fax to an authorized distributor. Annually, the authorized representative's name and contact information will be verified to ensure it corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, a new authorized representative must certify for the pharmacy. All reference to the requirement in the 2021 Mifepristone REMS Program that mifepristone to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber, and not from retail pharmacies, was removed.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes are in line with the REMS Modification Notification letters sent December 16, 2021. Refer to section 3.3.2.3 Reviewer Comments on Pharmacy Certification for rationale for removing the statement that mifepristone is not distributed to or dispensed from retail pharmacies. Ensuring that the authorized representative's contact information is up to date is necessary to ensure that there is always a point person who is responsible for implementing the Mifepristone REMS Program in their pharmacy and can address any changes that are needed if pharmacy audits identify a need for improvement.*

3.3.3.3. Sponsor Implementation Requirements

The Sponsors proposed that they will ensure that adequate records are maintained to demonstrate that REMS requirements have been met (including but not limited to records of mifepristone distribution, certification of prescribers and pharmacies, and audits of pharmacies and distributors), and that the records must be readily available for FDA inspections. The distributor audit requirement was updated to audit new distributors within 90 calendar days of becoming authorized and annually thereafter (a one-time audit requirement was previously required). The Sponsors also proposed a pharmacy audit requirement whereby certified pharmacies that order mifepristone are audited within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter for pharmacies that ordered in the previous 12 months.

Reviewer's Comment: *We agree with the Sponsors' proposal.*

The number of pharmacies that will certify in the REMS is uncertain; therefore, to obtain a reliable sample size for the audits, the Sponsors will need to audit all certified pharmacies within 180 calendar days after the pharmacy places its first order and annually thereafter for pharmacies that have ordered mifepristone in the previous 12 months. Audits performed at 180 days should allow time for establishment and implementation of audit protocols and for the Sponsors to perform the audits. With the addition of more stakeholders (i.e., certified pharmacies), it is also necessary to audit distributors annually to ensure the REMS requirements are followed. The requirement to conduct audits annually may be revisited if assessment data shows that the REMS is meeting its goal.

3.4. REMS Assessment Timetable

The Sponsors proposed that assessments must be submitted one year from the approval of the modified REMS and annually thereafter, instead of every three years as per the previous requirement.

***Reviewer's Comment**: We agree with the Sponsors' proposal. With the addition of new pharmacy stakeholders and removal of the in-person dispensing requirement, more frequent assessment after this REMS modification is needed to ensure REMS processes are being followed and that the REMS is meeting its goal. The requirement can be revisited at a later date if assessment data shows that the modified REMS is meeting its goal. The NDA applicant is required to submit assessment reports as outlined in the timetable for submission of assessments. These reports address requirements for the Mifepristone REMS Program. The Sponsors have indicated that some data will be submitted as separate reports when Sponsor-specific information is needed to address the assessment metrics.*

4. Supporting Document

The Sponsors' REMS Supporting Document was substantially updated to include information regarding the proposed modification under review. Background and rationale from the 12/16/21 REMS Modification Notification letters was included. An updated description of the REMS goal and the ETASU was also included to align with the changes in the REMS Document and provide further clarification. Further explanation of prescriber requirements and rationale for various pharmacy requirements was also included.

Regarding implementation of the modified REMS, the Sponsors additionally proposed that pharmacies that received and shipped mifepristone during the Agency's exercise of enforcement discretion during the COVID-19 PHE, that wish to continue to dispense mifepristone, will be required to comply with the pharmacy certification requirements within 120 days of approval of the modified REMS.

The communication strategy to alert current and future prescriber and pharmacy stakeholders was outlined. Distributors, certified prescribers that purchased mifepristone in the last twelve months, and various professional organizations will receive information about REMS changes within 120 days of modification approval. The Sponsors proposed to list pharmacies that agree to be publicly disclosed on their respective product websites but disclosure of this nature is not a requirement of the REMS. The Sponsors indicated that they anticipate certified pharmacies that do not agree to public disclosure will communicate with the certified prescribers they wish to work with.

The REMS Assessment Plan is discussed in the following section.

***Reviewer's Comment**: We agree with the Sponsors' proposal. The Supporting Document addresses all REMS requirements and provides sufficient clarification of implementation and maintenance of the REMS. The implementation requirements for pharmacies currently dispensing mifepristone under FDA's exercise of enforcement discretion during the COVID-19 PHE provide for continued use of these pharmacies without breaks in service. The communication strategy is also adequate given the efforts to reach both established certified prescribers and potentially new prescribers through professional organizations.*

The Sponsors' plan to communicate which pharmacies are certified to certified prescribers is adequate. For the reasons listed in section 3.3.2.3, confidentiality is a concern for REMS stakeholders. Disclosure of pharmacy certification status should be a choice made by individual certified pharmacies. The Sponsors have indicated that there will be some certified pharmacies that have agreed to publicly disclose their status, making this information available to certified prescribers who wish to use a pharmacy to dispense mifepristone.

5. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter.

The REMS Assessment Plan was revised to align with the modified REMS goal and objectives.

The goal of the Mifepristone REMS Program 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.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

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.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

c. Informing patients about the risk of serious complications associated with mifepristone.
    - This objective will be indirectly assessed using REMS Certification Statistics to avoid compromising patient and prescriber confidentiality. As part of the certification process, healthcare providers agree to:
        - Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained
        - Ensure that the *Patient Agreement Form* is signed by the healthcare provider and the patient
        - Ensure that the patient is provided with a copy of the *Patient Agreement Form* and the Medication Guide
        - Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record

The following revisions were made from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval letter:

The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.

REMS Certification Statistics metrics were added to capture certification numbers for program stakeholders to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. The total number of certified prescribers who certified with the wholesaler/distributor and the total number of certified prescribers who submitted a *Prescriber Agreement Form* to certified pharmacies were added to capture the additional method of prescriber certification. The number of newly certified prescribers and the number of active certified prescribers (i.e., those who ordered mifepristone or submitted a prescription during the reporting period) were added. Metrics were also added to capture the total number of certified, newly certified, and active certified pharmacies as well as the total number of authorized, newly authorized, and active authorized wholesaler/distributors.

Drug Utilization Data metrics were added to obtain information on shipment and dispensing of mifepristone. Metrics were added to capture the total number of tablets shipped by the wholesaler/distributor and the number of prescriptions dispensed.

REMS Compliance Data metrics were added to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. These metrics capture program deviations and evaluate overall if the REMS is operating as intended. Metrics include certified pharmacies and wholesaler/distributor audit results and a summary of instances of non-compliance and actions taken to address non-compliance. Prescriber compliance metrics were added to assess if prescribers are decertified along with reasons why. Pharmacy compliance metrics were added to assess if prescriptions were dispensed that were written by non-certified prescribers or if mifepristone tablets were dispensed by non-certified pharmacies as well as the number of pharmacies that were decertified along with reasons why. Wholesaler/distributor metrics were added to assess if shipments were sent to non-certified prescribers and non-certified pharmacies and corrective actions taken. The audit plan and non-compliance plans will be submitted for FDA review within 60 days after the REMS modification approval.

The Sponsors were asked to develop an assessment of prescription delivery timelines to determine what percentage of prescriptions were delivered on time (within four calendar days) and what percentage were delivered late (more than four calendar days) along with the length of the delay and reasons for the delay (e.g., mifepristone is out of stock shipment issues, other). The protocol for this assessment will be submitted for FDA review within 60 days after the REMS modification approval.

The revised REMS Assessment Plan is in the Appendix.

Reviewer's Comment*: We agree with the Sponsors' proposed REMS Assessment Plan.*

6. Discussion

The Sponsors submitted changes to the REMS to remove the requirement that mifepristone be dispensed only in certain healthcare settings (i.e., the "in-person dispensing requirement") and to add that certified pharmacies can dispense the drug in order to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. The REMS goal was updated to this effect. Changes were required for prescriber requirements and Sponsors to support the change in ETASU, and new pharmacy requirements were introduced.

The qualifications to become a certified prescriber have not changed as a result of the modification to the Mifepristone REMS Program; however, clarification has been provided for certain prescriber requirements and new prescriber requirements have been added to support pharmacy dispensing. Although certain responsibilities may be conducted by staff under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. In order to clarify this, revisions were made throughout the prescriber requirements and REMS materials to reflect that the certified prescriber is responsible for ensuring that the prescriber requirements are met. Additionally, the review team finds it acceptable that certified prescribers who wish to use a certified pharmacy to dispense mifepristone submit their *Prescriber Agreement Form* to the dispensing certified pharmacy (b) (4) . The burden to prescriber and

pharmacy stakeholders of having certified prescribers submit the form directly to the certified pharmacy that will be dispensing the mifepristone is not unreasonable and has been minimized to the extent possible; it does not impact the safe use of the product. Prescriber requirements necessitated by the addition of some pharmacy requirements were added as well and include prescriber responsibilities in deciding whether or not mifepristone should be dispensed if the patient will receive the drug from the certified pharmacy more than four days after the pharmacy receives the prescription, and prescriber adverse event reporting requirements if a prescriber becomes aware of a patient death and the mifepristone was dispensed from a certified pharmacy. The addition of the latter requirements will ensure consistent adverse event data is relayed to the relevant Mifepristone Sponsor.

Changes were made to the *Patient Agreement Form.* Changes to the form were added to improve clarity of the safety messages. After further consideration, the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion has been removed from the *Patient Agreement Form*. The Medication Guide is not typically carried by patients and this information can be obtained at the point of care. Changes align with updates to labeling submitted with this modification.[13, 14]

The Agency and Sponsors agreed during this modification to focus on certification of pharmacies that can receive *Prescriber Agreement Forms* via email or fax to complete the prescriber certification process. The proposed pharmacy certification requirements also support timely dispensing of mifepristone. If the mifepristone is shipped to the patient, the REMS requires that it must be delivered within four calendar days from the receipt of the prescription by the pharmacy; if the patient will receive the mifepristone more than four calendar days from pharmacy receipt of prescription, the REMS requires the pharmacist to confirm with the certified prescriber that it is still appropriate to dispense the drug to the patient. This allows prescribers to make treatment decisions based on individual patient situations. A requirement to maintain confidentiality was also added to avoid unduly burdening patient access since patients and prescribers may not utilize pharmacy dispensing if they believe their personal information is at risk. Ultimately, the addition of pharmacy distribution with the proposed requirements will offer another option for dispensing mifepristone, alleviating burden associated with the REMS.

(b) (4)

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The Agency reviewed the REMS in 2021, and per the review team's conclusions, a REMS modification was necessary to remove the in-person dispensing requirement and add a requirement that pharmacies that dispense the drug be specially certified; the review team concluded that these changes could occur without compromising patient safety. There have been no new safety concerns identified relevant to the REMS ETASUs that the applicants proposed modifying in their June 22, 2022 submissions since the REMS Modification Notification letters dated 12/16/2021. It is still the position of the review team that the proposed modification is acceptable.

Because the modification proposed include changes to the ETASU of the Mifepristone REMS Program, the assessment plan and timetable of assessments were changed. The assessment plan will capture information on pharmacy dispensing and provide valuable insight as to whether the program is operating as intended Annual assessments are consistent with other approved REMS modifications for major modifications necessitating extensive assessment plan changes.

As part of the REMS Assessment Plan, the REMS goal and objectives are assessed using Program Implementation and Operations Metrics, including REMS Certification Statistics and REMS Compliance Data. The metrics will provide information on the number of certified prescribers, certified pharmacies, and authorized wholesalers/distributors as well as if mifepristone is dispensed by non-certified prescribers or pharmacies. The Sponsors will use the indirect measure of healthcare provider certification to address the objective of informing patients of the risk of serious complications of mifepristone, due to concerns with prescriber and patient confidentiality. Although we typically assess whether patients are informed of the risks identified in a REMS through patient surveys and/or focus groups, we agree that the Sponsors' continued use of the indirect measure of healthcare provider certification adequately addresses the Mifepristone REMS Program objective of informing patients. In addition, because of these prescriber and patient confidentiality concerns, we believe it is unlikely that the Agency would be able to use the typical methods of assessment of patient knowledge and understanding of the risks and safe use of mifepristone.

7. Conclusions and Recommendations

The review team finds the proposed REMS modification for the Mifepristone REMS Program, as submitted on June 22, 2022, and amended on October 19, 2022 (Danco) and October 20, 2022 (GBP), November 30, 2022 (both), December 9 (both), and December 16 (both) acceptable. The REMS materials were amended to be consistent with the revised REMS document. The review team recommends approval of the Mifepristone REMS Program, received on June 22, 2022, and last amended on December 16, 2022, and appended to this review.

8. References

1. (b) (6) Clinical Review of SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909590.

2. (b) (6) Summary Review for Regulatory Action for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909594.

3. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909588.

4. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909587.

5. Approval Letter for SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909592.

6. (b) (6) REMS Review for mifepristone, NDA 020687. February 22, 2018. DARRTS Reference ID: 4224674.

7. Approval Letter for SE-20 REMS Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 4418041.

8. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the

Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

9. (b) (6) REMS Modification Rationale Review for mifepristone, NDA 020687. December 16, 2021. DARRTS Reference ID: 4905882.

10. General Advice Letter for the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, NDA 020687, April 15, 2022. DARRTS ID 4969358.

11. Format and Content of a REMS Document Guidance for Industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf. Accessed on December 18, 2022.

12. Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2022; 107:36-41. https://doi.org/10.1016/j.contraception.2021.09.008. This article was included in the literature review for the December 16, 2021 REMS Modification Rationale Review, while the article was still in press.

9. Appendices

REMS Document

Prescriber Agreement Form for Danco Laboratories, LLC

Prescriber Agreement Form for GenBioPro, Inc.

Patient Agreement Form

Pharmacy Agreement Form for Danco Laboratories, LLC

Pharmacy Agreement Form for GenBioPro, Inc.

Mifepristone REMS Assessment Plan

Suppl. Ex. B

U.S. Food & Drug Admin., REMS Review Memorandum (Dec. 16, 2021)

Center for Drug Evaluation and Research (CDER)

(b) (6)

Application Type	NDA and ANDA
Application Number	020687 and 91178
Reviewer Names	(b) (6)
	(b) (6)
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	(b) (6)
Review Completion Date	December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

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EXECUTIVE SUMMARY

This review provides the [redacted] rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the "in-person dispensing requirement" for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[a] This review provides the analysis of the (b) (6) ((b) (6) and the (b) (6) ((b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

[a] Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

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 (under ETASU A).
b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone 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. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.

- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.

- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.

- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.[c]

- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.

- 1/12/2021: US Supreme Court granted a stay of that injunction.

- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

[c] *See* Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form.* FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.

- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.

- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.

- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.

- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.[d]

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- (b) (4)
- 11/02/2021: A (b) (6) ((b) (6) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The (b) (6) (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

[d] Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.

- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.

- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.

- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)

- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.

- Publications that provided only general statistics on abortion care in the United States.

- Information pertinent to molecular or other basic science aspects of mifepristone.

- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.

- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the *Patient Agreement Form*.
- Provide the patient with a copy of the *Patient Agreement Form* and the Medication Guide.
- Place the signed *Patient Agreement Form* in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

pregnancy, to diagnose an ectopic pregnancy,[e] and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

[e] American College of Obstetricians and Gynecologists (ACOG) Practice Bulleting Number 191, February 2018. Tubal Ectopic Pregnancy. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[f]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6) ((b) (6)), along with the (b) (6) ((b) (6)), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 review[g] is summarized here as follows:

- 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 evidence shows that practitioners are providing appropriate patient

[f] REMS@FDA, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.
[g] (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803dc7bd&_afrRedirect=386175573203745

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the (b) (6) March 29, 2016 review and a memorandum from the signatory authority in (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.[h,i]

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies[1,2] (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong[3], Kerestes[4]). Aiken[5] reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca[6] described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

h (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.
i (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe[7]) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent "witnessed by the counselor". Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient's informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation's 2020 Clinical Policy Guidelines for Abortion Care[8] continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG[9] and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017[10] of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman[11] conducted a US survey in

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/ gynecologists by Daniel in 2021[12] evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% −112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% −207%) and the South (+ 118%, 95% CI: 103% −134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)[j] REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.[13] The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

[j] This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the *ACOG* case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.[k,l]

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.[m,n] (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of 12 of the 13

[k] FDA General Advice Letter for NDA 20687, April 12, 2021.
[l] FDA General Advice Letter for ANDA 091178, April 12, 2021.

[m] NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.
[n] NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Mifeprex tablets to the distributor. [redacted] non-certified healthcare provider dispensed one tablet to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed [redacted] shipments representing [redacted] tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The [redacted] ([redacted]) conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.[o,p]

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

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[o] [redacted]. Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. [redacted] # 2007-525. Finalized April 12, 2021.

[p] [redacted] Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. [redacted] # 2007-525. Finalized December 16, 2021.

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6)

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested[q] to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

[q] On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).[r]

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

[r] The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.[s]

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman[2], Wiebe[7], Rocca[6]) and dispensing mifepristone from pharmacies by mail (Grossman[1], Upadhyay[14], Hyland[15]). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond[16], Chong[3], Anger[17]], Kerestes[4], Aiken[5] (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright[18]). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken[19] (2017), Norton[20], Endler[21]). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman[2] conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

[s] The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca[6] conducted an observational study evaluating 605 participants at ≤63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion (>97%) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[7] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; ≥ 95% calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman[2]), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe[7]) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service[t] which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca[6] study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman[1] published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

[t] As noted in Mark[23] and Martin[24], most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay[14] reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[15] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up". The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman[1] study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland[15] study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay[14] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.[3,4,5,16, 17] Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

exclusively: Raymond[16] from May 2016 to December 2018, Chong[3] from May 2016 to September 2020 and Anger[17] from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,[4] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken[5] (2021).

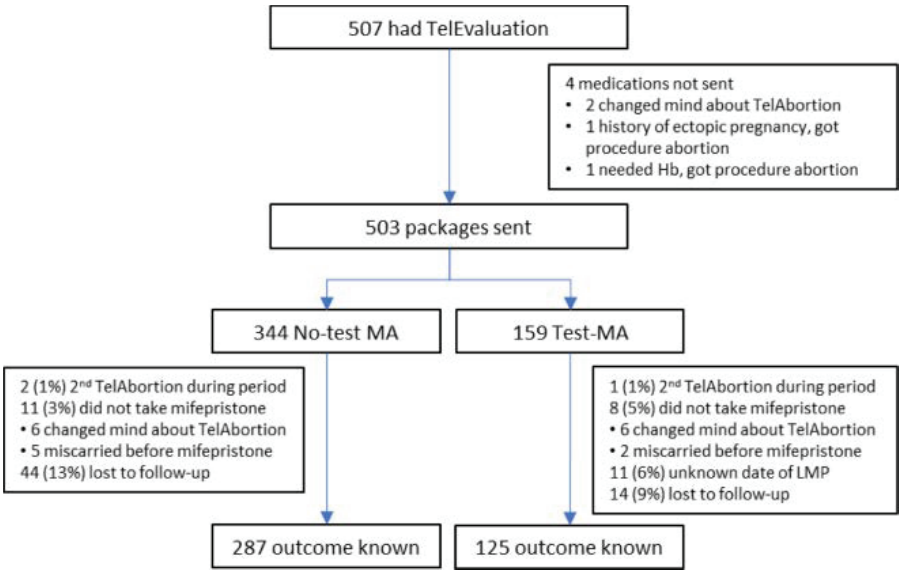
Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond[16] (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.[16] All participants received medications within 8 days.

Chong[3] updated the findings from the Gynuity study described in Raymond[16] and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger[17] compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"[u] based on a sample protocol published by Raymond[22] (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

[u] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.[22]



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes[4] was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports[3,16,17] and Kerestes[4] support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond[16], Chong[3]) and Kerestes[4] report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken[5] (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion[u] (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken[5] (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),[3,16,17] Kerestes[4], and Aiken[5] (2021) support that efficacy of medical abortion was maintained. The Aiken[5] study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond[16] Chong[3], and Kerestes[4] all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's[17] comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond[16] publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond[16] reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright[18] reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken[5] (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail.[v] Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken[19] (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort's GA (almost 80% less than 7 weeks, labeled success for medical abortion ≤ 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants' self-reporting.

[v] In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Endler[21] and Norten[20] have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler[21] compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the "first or second day of abortion" that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten[20] describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken[19] (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.[w]

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

[w] *The Patient Agreement Form* can be signed in person or through other means.

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications[x] that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by "partner organizations". The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

[x] The 15 publications correspond to endnote numbers: 1-7, 14-21.

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond[16], Chong[3], Anger[17] and Kerestes[4]), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond[16]), may be associated with participants being located significant distances from their providers. The Aiken[5] (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman[1] and Hyland[15], where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's[1] interim analysis found no increases in SAEs. Hyland[15] reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.[j,y,z] Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

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y ANDA 091178: September 23, 2021 response to the September 15, 2021 information request; October 11 and 16, 2021 responses to the June 30, 2021 and July 15, 2021 information requests; October 26, 2021 response to the October 22, 2021 information request; October 29, 2021 response to the October 27 information request.
z NDA 020687: September 20, 2021 response to the September 15, 2021 information request; October 26, 2021 response to the October 22 information request.

when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients. As modified, the REMS would allow, for example, dispensing by mail order or specialty pharmacies, similar to the distribution model used by applicants during the periods when the in-person dispensing requirement was not being enforced.[aa]

The above recommendations were discussed with the (b) (6) ((b) (6) and senior leadership from CDER on November 2, 2021. The (b) (6) (b) (6) along with senior CDER leadership, concurred with removing the in-person dispensing requirement provided that all of the remaining REMS requirements are met, including but not limited to prescriber certification where prescribers need to attest to having certain qualifications, and maintaining the *Patient Agreement Form*. The (b) (6) (b) (6) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

[aa] Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

6. References

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7. Appendix A

References Cited in Letters from Plaintiffs

References cited in letter from *Chelius v. Becerra* Plaintiffs (September 29, 2021)	
References included in the REMS review	
Aiken A et al. BJOG 2021: 128 (9): 1464-1474	
Chong, et al. Contraception 2021; 104(1) 43-48	
Daniel S. et al. Contraception 2021; 104(1): 73-76	
References excluded from the REMS review	**Rationale for Exclusion**
Am. Coll. of Obstetricians & Gynecologists, *Position Statement: Improving Access to Mifepristone for Reproductive Health Indications* (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications	Policy/advocacy statement
House of Delegates, Am. Med. Ass'n., *Memorial Resolutions Adopted Unanimously No. 504 (2018)* https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf	Policy/advocacy statement
Cong. Of Delegates, Am. Acad. Of Fam. Physicians, *Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization of Mifepristone* (May 24, 2018) https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf	Policy/advocacy statement
Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625 Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96 Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235 Barr-Walker J, et al PLoS One 2019;14(4): e0209991 Grossman et al JAMA Network 2017;317(4):437, 437-438 Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244 Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262 Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232 Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689	Focused on the logistics of accessing abortion care.
CDC MMWR Abortion Surveillance – United States, 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down	Contains primarily general statistics on abortion care by state.

References cited in appendix from *Chelius v. Becerra* Plaintiffs (September 29, 2021)
References included in the REMS review
None

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

References cited in letter from Society of Family Planning (August 11, 2021)
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Chen MJ et al. Obstet Gynecol 2015;126(1):12-21 reviewed in 2016 memo	
Chong et al. Contraception 2021;104(1): 43-48	
Aiken A et al. BJOG 2021; 128 (9): 1464 -1474	
Hyland 2018 et al. Aust New Zeal J Obstet Gynaecol 2018; 58 (3): 335-340	
References excluded from the REMS review	**Rationale for Exclusion**
Schummers L et al. BMJ Sex Reprod Heal 2021;47(e1)	Abstract
Kapp et al. 2020 (as above)	Abstract
Upadhyay et al. 2015 (as above)	(See rationale above)
Srinivasulu et al. Contraception 2021; 104(1):92-97	Survey on clinician perspectives on access to mifepristone.
Calloway D et al. Contraception 2021; 104(1): 24-28	Primarily addresses provider stigma around abortion care.
Rasmussen et al. Contraception; 104(1): 98-103	Opinion/commentary
Cleland et al. Obstet Gynecol 2013;121(1):166-171	Published prior to March 29, 2016 - July 26, 2021 timeframe for current literature review. We note that the extensive literature search conducted as part of the 2016 clinical review, which was consistent with the division's standard approach for reviewing an efficacy supplement and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
National Academy of Sciences, Engineering, and Medicine. Safety and Quality of Abortion Care in the US 2018	General information about abortion care in the US. Did not provide safety data relevant to the elements of the REMS
Raymond EG. Obstet Gynecol 2012: 119(2): 215-219	Does not separate out medical and surgical abortion.

Bartlett LA et al. Obstet Gynecol 2004; 103(4): 729-737	Focused on surgical abortion.
Jones RK, Jerman J. Time to appointment and delays in accessing care among U.S. abortion patients, Guttmacher 2016	Focused on logistics of accessing abortion care.
Foster DG et al. Perspect Sex Reprod Health 2013; 45(4):210-218	Focused on second trimester abortion.
Ely G et al. Heal Soc Work 2019;44(1):13-21	Focused on logistics of accessing abortion care.
Munro S et al. Ann Fam Med 2020; 18(5):413-421.	Survey on physician perspectives on implementing medical abortion with mifepristone.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Suppl. Ex. C

Letter from *Chelius* Plaintiffs to Janet Woodcock, MD (Sept. 29, 2021)

Sept. 29, 2021

BY ELECTRONIC MAIL

Janet Woodcock, M.D.
Acting Commissioner
United States Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Re: Evidence Supporting Elimination of the Mifepristone REMS

Dear Dr. Woodcock:

We are the health care providers and researchers engaged in litigation challenging the Risk Evaluation and Mitigation Strategy ("REMS") for mifepristone 200 mg for termination of early pregnancy. We are pleased that the U.S. Food and Drug Administration ("FDA") has initiated a comprehensive evaluation of the mifepristone REMS and its three elements to assure safe use ("ETASU"), and appreciate the opportunity to submit data and evidence for FDA's review.[1]

As you know, it is our position that a REMS is not medically necessary to ensure that the benefits of mifepristone outweigh its risks.[2] We note that one of the signatories to this letter (the Society of Family Planning) is the organization that represents Complex Family Planning Fellowship-trained obstetrician-gynecologists, who are the leaders in clinical care, medical education, and research relating to abortion and contraception. Other leading medical authorities—including the American Medical Association, the American College of Obstetricians and Gynecologists, and the American Academy of Family Physicians—likewise support eliminating these restrictions.[3] We hope that, following a comprehensive evaluation incorporating new data and evidence from the past five years, FDA will reach the same conclusion.

The Mifepristone REMS with ETASU Does Not Enhance Safety

As extensively detailed in the letter submitted by the Society of Family Planning on August 11, 2021, peer-reviewed scientific evidence, including research published since the most recent FDA-approved labeling change in 2016, confirms that mifepristone is extremely safe and highly effective whether dispensed at a health center, pharmacy, or by home delivery, and does not require a clinician to oversee dispensing or specially certify their ability to provide appropriate care. The evidence is clear that the mifepristone REMS and its three ETASU confer no benefit in terms of safety, efficacy, or acceptability of the medication, are not "commensurate with" the risks of mifepristone,[4] and create barriers to use that reduce patient access and negatively impact public health, causing particular harm to communities of color, people with fewer resources, and people living in rural areas.

Mifepristone's strong safety and efficacy findings hold true across a range of regulatory contexts, including international and domestic studies operating outside of the ETASU C dispensing framework. For instance, as you are aware,[5] a recent large (N=52,218) retrospective cohort study reported on the safety, efficacy, and acceptability of telemedicine abortion at Britain's

largest abortion providers, which rapidly adapted to provide medication abortion using telemedicine during the spring and summer of 2020 in response to the COVID-19 pandemic.[6] Following a telehealth consultation, individuals with a last menstrual period dating the pregnancy up to 69 days and without symptoms of ectopic pregnancy were able to receive both mifepristone and misoprostol by mail for home administration. Aiken and colleagues found that medication abortion was equally effective in this telemedicine model (98.8%) versus the traditional in-clinic mifepristone administration model (98.2%, p=1.0); that 99.98% of patients using the telemedicine model experienced no serious adverse events compared to 99.96% of abortions with an in-person assessment; and that patients obtaining their medications by mail following a telemedicine consultation were able to initiate treatment *earlier* in pregnancy than patients utilizing the traditional in-clinic model. Similarly, in a large (N=1,157 abortions) national U.S.-based clinical trial of mifepristone dispensing by mail (the TelAbortion study), Chong and colleagues found that mifepristone dispensing by direct mail to consumers is effective (95% abortion completion with medication alone), with only 0.9% experiencing any serious adverse event, compared to a serious adverse event rate of 0.65% in a large (N=233,805 medication abortions) retrospective cohort study of in-clinic mifepristone administration.[7]

There is likewise no evidence that the ETASU A requirement that mifepristone prescribers attest to their ability to prescribe mifepristone mitigates any safety risks of the medication. Indeed, the evidence refutes this. For instance, in Canada, mifepristone-specific requirements for provider certification were lifted in November 2017. According to a comprehensive analysis of linked medical and financial records in Ontario, medication abortion remained extremely safe after deregulation, with a major complication rate of 0.33% compared to a rate of 0.31% in an analysis of a similar administrative dataset from California under the REMS, and consistent with a clinical review finding major complication rates below 1% across multiple studies of mifepristone use for early abortion.[8]

Finally, we agree with the recommendation of FDA's scientific review team in 2016 to eliminate ETASU D, after finding that this ETASU "does not add to safe use conditions" because the Patient Agreement is "generally duplicative of information contained 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."[9]

The Mifepristone REMS Is an Outlier and Unwarranted by Mifepristone's Strong Safety Record

Consistent with strict statutory criteria,[10] FDA imposes REMS programs rarely: fewer than 3% of FDA-regulated drugs are subject to a REMS,[11] and the overwhelming majority of drugs subject to a REMS are opioids—which, in FDA's words, are "claiming lives at [such] a staggering rate" that they are "reducing life expectancy in the United States."[12] FDA subjects only 17 drugs (0.09%), including Mifeprex® and its generic, to a REMS requiring the patient to obtain the medication in a clinic, office, or hospital.[13] And for all such drugs *except* mifepristone, FDA also requires that the medication be taken under clinical supervision, either because of the administration form (e.g., intravenous) or because it can be safely administered only in certain settings (e.g., with monitoring for immediate reactions such as "life-threatening respiratory depression"). In short, mifepristone is the only drug in the nation that FDA requires patients to

pick up in a clinical setting yet permits patients to self-administer elsewhere without direct clinical supervision, based on data confirming the safety of home administration.[14]

While we recognize that there are multiple factors informing the determination of whether a REMS is necessary for any individual drug,[15] we note that FDA has determined that many other drugs posing risks of serious adverse events can be successfully regulated through labeling without a REMS. For example:

- Jeuveau® is an FDA-approved acetylcholine release inhibitor and a neuromuscular blocking agent "indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients"—i.e., it is indicated for a purely cosmetic purpose among a healthy population. Jeuveau carries a black-box warning for "[s]wallowing and breathing difficulties" that "can be life threatening" if this botulinum toxin product spreads beyond the area of injection, and the labeling notes that "there have been reports of death."[16]
- Propecia®, a drug "indicated for the treatment of male pattern hair loss," had its labeling updated in 2011 to reflect that this cosmetic medication may cause an "increased risk of high-grade prostate cancer."[17]
- NuvaRing® is an estrogen/progestin combination hormonal contraceptive ("CHC") inserted as a vaginal ring, which carries a black-box warning for "serious cardiovascular events" with increased risk among cigarette smokers.[18] Its labeling warns patients that CHCs pose a risk of "death from heart attack, blood clots or stroke."[19] Other serious risks associated with NuvaRing include Toxic Shock Syndrome and liver tumors.[20]
- Coumadin®, a common anticoagulant, carries a black box warning for "major or fatal bleeding," with risk ranging from 0.6 to 4.6% for patients with certain comorbidities.[21]

For all of these drugs, FDA has determined that the benefits outweigh the risks even in the absence of a REMS. Now, with the benefit of additional safety and efficacy data on mifepristone reported over the past five years, we urge you to find that mifepristone's risks likewise can be appropriately managed through labeling without a REMS.

The Mifepristone ETASU Are Unduly Burdensome

The REMS statute prohibits ETASU that are "unduly burdensome on patient access to the drug, considering in particular . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)."[22] The statute further requires that any ETASU be crafted to "minimize the burden on the health care delivery system," "[t]o the extent practicable."[23]Accordingly, FDA has emphasized that a "REMS should be designed to meet the relevant goals, not unduly impede patient access to the drug, and minimize the burden on the health care delivery system to the extent practicable."[24] While a drug sponsor may request changes to a REMS program, it is FDA that is responsible for ensuring that any REMS comports with all statutory and regulatory requirements and limitations, regardless of what the sponsor has proposed or requested.[25]

The mifepristone ETASU do not comply with these requirements. Extensive evidence shows that these ETASU significantly impede patient access, and do so in part by burdening health care providers. And, whereas FDA has long acknowledged that mifepristone is "important to the health of women,"[26] has underscored the need to prevent treatment delays for mifepristone patients,[27] and has stressed that unwanted pregnancy can be a "serious medical condition,"[28] substantial evidence shows that the mifepristone ETASU *cause* treatment delays and prevent some pregnant patients from obtaining a desired abortion at all.

Attached as appendices are several declarations that were submitted as part of the *Chelius v. Becerra* litigation, which provide first-hand physician narratives, research, and statistical analysis detailing how the mifepristone ETASU unduly burden the health care delivery system and patients' access to this medication. We appreciate your consideration of all of this relevant evidence, which we briefly summarize below:

First, the mifepristone ETASU reduce the pool of qualified clinicians providing medication abortion, including in the geographic areas most lacking in abortion access. For instance, in a nationally representative survey of currently practicing board-certified obstetrician-gynecologists, fewer than one in five respondents who see patients seeking abortion care reported having provided a medication abortion during the previous year—but the proportion of medication abortion providers would likely *double* if clinicians were permitted to prescribe mifepristone through a pharmacy.[29] Notably, the number of respondents in the South and Midwest who said they would begin providing medication abortion if not for the REMS was higher than the number who were currently providing such care.[30] This finding is of particular significance given the increasing efforts by states in the South and Midwest to ban abortion at all but the earliest weeks of pregnancy.[31] Put plainly, if there are more medication abortion providers in those states, more patients will be able to obtain abortions before confronting those (unconstitutional) gestational age limits. Moreover, while the overwhelming majority of current abortion providers practice in urban areas, 40% of OB-GYNs who responded that they would provide medication abortion care if not for the REMS identified their practices as "suburban" or "midsize town, rural, or military."[32]

Specifically, ETASU C burdens the health care delivery system and severely reduces patient access because of the challenges of obtaining institutional approval to dispense mifepristone onsite, and the complicated logistics necessary to do so. It is extremely unusual for health care providers to have to serve as, in effect, both prescribers and pharmacists; as noted above, fewer than 0.1% of FDA-approved drugs must be dispensed in a hospital, medical office, or clinic. Thus, health care institutions typically must develop unique protocols around the dispensing of mifepristone onsite, which can significantly delay clinicians' ability to prescribe this medication or prevent them from doing so at all. As just one example, it took five years and hundreds of hours of individual clinician and stakeholder advocacy before mifepristone was available to patients at the University of Michigan's Women's Clinic. After years of clinician lobbying to add mifepristone to the institution's formulary, personnel across the organization then had to develop protocols for ordering, storing, and dispensing the medication (including "opt-out" protocols for staff opposed to any involvement in such activities), as well as establish insurance and billing practices. Many clinicians would face none of these burdens if their patients could simply fill their mifepristone prescription through a retail or mail-order pharmacy.

Additionally, ETASU C exacerbates these logistical burdens by enabling interference by individuals opposed to abortion. Instead of being able to simply issue a mifepristone prescription for an eligible patient to fill at a pharmacy, clinicians seeking to prescribe mifepristone must—as a direct result of ETASU C—involve numerous other health care staff in the process of procuring, stocking, dispensing, and billing for mifepristone onsite. As a practical matter, this means that even a single colleague who objects to abortion can substantially delay, or altogether derail, a clinician's ability to prescribe a safe and effective medication that their patients urgently need.

ETASU A also deters many qualified clinicians from becoming mifepristone prescribers. In light of the long history of anti-abortion violence and harassment in this country, some physicians are unwilling to register with the mifepristone sponsors—fearful of what they and their families might face if abortion opponents were ever able to access their certification agreements. While the drug manufacturers and distributors are required to maintain that information strictly confidentially, these clinician fears are not unfounded; indeed, in our litigation, FDA was unwilling to provide Plaintiffs with the names or offices of agency staff who had been involved in any Mifeprex reviews, *even subject to a protective order* requiring strict confidentiality of Plaintiffs and their counsel.[33] Prescriber certification presents a real barrier to patient access, and, as discussed above, there is no evidence showing that this ETASU advances any countervailing safety interest sufficient to outweigh these burdens.

Second, ETASU C forces patients to travel unnecessarily to a mifepristone provider for no medical reason, and in sharp contrast with the expansion of telemedicine nationwide. Across virtually all other areas of medicine, a telemedicine revolution is increasing health care access in medically under-resourced communities and reducing the need for patients to travel long distances for care. But, while medically eligible mifepristone patients already can and do obtain all evaluation and counseling via telemedicine, the REMS prohibits patients from filling their prescription by mail or at a local pharmacy. Instead, FDA requires that mifepristone patients travel to a health center for the sole purpose of picking up the pill and signing a form.

It is important to understand that abortion access is very limited in the United States—in part due to the burdens of ETASU C and A, which reduce the number of clinicians able to provide this essential health care. A nationally representative sample of 8,000 abortion patients found that patients traveled, on average, 68 miles round-trip to receive an abortion.[34] In a majority of states, at least 20% of reproductive-age women live more than 100 miles round-trip from the nearest abortion clinic.[35] And while rural areas are particularly lacking, patients in urban areas also struggle. A 2018 study found that 27 major cities have no publicly advertised abortion provider within 100 miles.[36] Requiring patients to pick up their mifepristone pill in person at a health center thus in many cases requires significant travel.

Given the mifepristone patient population, such travel can be incredibly difficult and in some cases impossible. According to a nationally representative survey, in 2014 (the most recent year for which such data are available), 75 percent of abortion patients had incomes at or below the U.S. Official Poverty Measure.[37] Sixty percent of abortion patients identify as people of color, including 53 percent of patients who identify as Black or Hispanic.[38] And 60 percent of abortion patients have at least one child.[39] Forcing patients to travel in person to pick up the mifepristone tablet at one of the (few) abortion providers in the country imposes costs and burdens relating to

transportation, childcare, and lost wages for missed work that many in this patient population simply cannot afford. Indeed, a robust body of research, spanning multiple states and decades, confirms that forcing patients to travel even slightly farther (e.g., 10 miles) delays or blocks patients from accessing desired abortions.[40] In short, these ETASU specifically burden "patients who have difficulty accessing health care," in violation of the REMS statute.[41]

***

We welcomed FDA's April 2021 announcement that it intends to exercise enforcement discretion during the COVID-19 Public Health Emergency with respect to the dispensing of mifepristone through the mail or through a mail-order pharmacy when such dispensing is done by or under the supervision of a certified prescriber. We note that this enforcement discretion has mitigated some (though not all) of the burdens on patients and the health care delivery system described in the physician narratives attached as Appendices. Most significantly, enabling patients to obtain their mifepristone prescription through telemedicine and mail-order pharmacies where medically appropriate has prevented many patients from having to needlessly travel for health care during the pandemic, reducing treatment delays and COVID-19 risks and enabling some patients to access mifepristone who otherwise would not have been able to do so at all.

In addition, having the option to submit a prescription to a pharmacy and then have the pharmacy directly bill and dispense the mifepristone to their patient has enabled some qualified physicians—who previously had been impeded by the complex logistics and controversy around procuring, stocking, dispensing, and billing for mifepristone onsite at their health centers—to begin prescribing this medication for the first time. This is consistent with the nationally representative OB-GYN survey discussed above, which showed that eliminating the REMS would increase the pool of qualified mifepristone prescribers.[42] If the other barriers imposed by the mifepristone ETASU are lifted, even more qualified clinicians will be able to begin prescribing this safe and effective medication.

We appreciate FDA's careful consideration of the extensive evidence showing that the mifepristone REMS does not advance patient safety; causes treatment delays that undermine patients' health; subjects some patients who are unable to obtain mifepristone because of the REMS to the serious medical risks of ongoing pregnancy and childbirth; and unduly burdens both patients and the health care delivery system, with disproportionate harm to people living in rural and medically underserved areas, people with fewer financial resources, and people of color. Consistent with this sound evidence, we urge you to eliminate the mifepristone REMS.

Sincerely,

Dr. Graham Chelius
The Society of Family Planning
The California Academy of Family Physicians

Plaintiffs in *Chelius v. Becerra*, No. 1:17-cv-00493-JAO-RT (D. Haw.)

CC: Dr. Patrizia Cavazzoni, Center for Drug Evaluation and Research
Dr. Catherine Sewell, Center for Drug Evaluation and Research

[1] *Chelius v. Becerra*, No. 1:17-cv-00493-JAO-RT (D. Haw.) [hereinafter *Chelius v. Becerra*], Joint Motion to Stay Case Pending Agency Review 2, Dkt. 148.

[2] 21 U.S.C. § 355-1(g)(4)(B)(i).

[3] *See, e.g.*, House of Delegates, Am. Med. Ass'n, *Memorial Resolutions Adopted Unanimously* No. 504 (2018), https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf; Am. Coll. of Obstetricians & Gynecologists, *Position Statement: Improving Access to Mifepristone for Reproductive Health Indications* (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications; Cong. of Delegates, Am. Acad. of Fam. Physicians, *Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization on Mifepristone* (May 24, 2018), https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf.

[4] 21 U.S.C. § 355-1(f)(2)(A).

[5] *See* Letter from Janet Woodcock, M.D., Acting Commissioner of Food & Drug Admin., to Maureen G. Phipps, M.D., M.P.H., FACOG, and William Grobman, M.D., M.B.A. (Apr. 12, 2021), https://www.aclu.org/letter/fda-response-acog-april-2021.

[6] Abigail Aiken et al., *Effectiveness, Safety and Acceptability of No-Test Medical Abortion (Termination of Pregnancy) Provided Via Telemedicine: A National Cohort Study*, 128(9) BJOG 1464 (Aug. 2021), https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.16668.

[7] Erica Chong et al., *Expansion of a Direct-to-Patient Telemedicine Abortion Service in the United States and Experience during the COVID-19 Pandemic*, 104(1) Contraception 43 (July 2021), https://www.contraceptionjournal.org/article/S0010-7824(21)00091-3/fulltext; Kelly Cleland et al., *Significant Adverse Events and Outcomes after Medical Abortion*, 121(1) Obstetrics & Gynecology 166 (Jan. 2013), https://pubmed.ncbi.nlm.nih.gov/23262942/.

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[9] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Application Number 020687Orig1s020: Summary Review(s)* 25 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020SumR.pdf; U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Application Number 020687Orig1s020: Risk Assessment and Risk Mitigation Review(s)* Ref ID: 3909589 at 2 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RiskR.pdf.

[10] 21 U.S.C. § 355-1(a)(1).

[11] *Chelius v. Becerra*, Joint Stips. of Facts, Dkt. 140, ¶¶ 59–60.

[12] *Id.* at ¶¶ 59–60; U.S. Food & Drug Admin., *Opioid Medications* (Mar. 29, 2021), https://www.fda.gov/drugs/information-drug-class/opioid-medications.

[13] *Chelius v. Becerra*, Joint Stips. of Facts, Dkt. 140, ¶¶ 59, 61.

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[15] 21 U.S.C. § 355-1(a)(1).

[16] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Application Number 761085Orig1s000: Labeling* (Jeuveau) (Feb. 2019), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761085Orig1s000Lbl.pdf.

[17] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Labeling* (Propecia) (Apr. 2012), https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020788s020s021s023lbl.pdf.

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[20] *Id.*

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[22] 21 U.S.C. § 355-1(f)(2)(C).

[23] 21 U.S.C. § 355-1(f)(2)(D).

[24] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., Ctr. for Bio. Eval. & Res., *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* 5 (April 2019), https://www.fda.gov/media/100307/download.

[25] 21 U.S.C. § 355-1(a), (d), (f).

[26] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Mifeprex (mifepristone) NDA Approval Letter* 4 (Sept. 2000), *Chelius v. Becerra*, Dkt. 142-2, Ex. B.

[27] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Final Risk Evaluation and Mitigation Strategy (REMS) Review: Mifeprex* (Oct. 2013), *Chelius v. Becerra*, Dkt. 85-8.

[28] Letter from Janet Woodcock, M.D., Director, Ctr. for Drug Eval. & Res., to Donna Harrison, M.D. et al., Denying Citizen Petition Asking the FDA to Revoke Approval of Mifeprex 4-5 (Mar. 29, 2016) (emphasis added), https://www.regulations.gov/document?D=FDA-2002-P-0364-0002.

[29] Sara Daniel et al., *Obstetrician-Gynecologist Willingness to Provide Medication Abortion with Removal of the In-Person Dispensing Requirement for Mifepristone*, 104(1) Contraception 73 (July 2021), https://www.contraceptionjournal.org/article/S0010-7824(21)00098-6/fulltext.

[30] *Id.*

[31] *See, e.g.*, *Whole Woman's Health v. Jackson*, No. 21A24, 2021 WL3910722 (U.S. Sept. 2, 2021) (denying request to block Texas's six-week abortion ban from taking effect); *Planned Parenthood S. Atl. v. Wilson*, No. 3:21-24 00508-MGL, 2021 WL 672406, at *2 (D.S.C. Feb. 29, 2021) (preliminary injunction of South Carolina six-week ban), *appeal filed*, No. 21-1369 (4th Cir. Apr. 5, 2021); *SisterSong Women of Color Reprod. Justice Collective v. Kemp*, 472 F. Supp. 3d 1297, 1312 (N.D. Ga. 2020) (preliminary injunction of Georgia six-week ban), *appeal filed*, No. 20-13024 (11th Cir. Aug. 11, 2020); *Memphis Ctr. for Reprod. Health v. Slatery*, No. 3:20-CV-00501, 2020 WL 4274198, at *2 (M.D. Tenn. July 24, 2020) (preliminary injunction of Tennessee six-week ban), *appeal filed*, No. 20-5969 (6th Cir. Aug. 24, 2020); *Preterm-Cleveland v. Yost*, 394 F. Supp. 3d 796, 804 (S.D. Ohio 2019) (preliminary injunction of Ohio six-week ban); *EMW Women's Surgical Ctr., P.S.C. v. Beshear*, No. 3:19-CV-178-DJH, 2019 WL 1233575, at *2 (W.D. Ky. Mar. 15, 2019) (temporary restraining order of Kentucky six-week ban).

[32] Daniel et al., *supra* n.29.

[33] *Chelius v. Becerra*, Joint Stips. of Facts, Dkt. 140, ¶ 47 ("In light of the violence and harassment surrounding the provision of abortion, FDA withheld FDA employee names and other identifying information from documents related to Mifeprex in the administrative record . . . . Because releasing this information would constitute an unwarranted invasion of personal privacy and could expose those employees to threats, intimidation, harassment and/or violence, FDA believes it is necessary not to disclose information that could be used to identify these employees to any person outside of FDA, including Plaintiffs' counsel subject to a protective order.").

[34] Liza Fuentes & Jenna Jerman, *Distance Traveled to Obtain Clinical Abortion Care in the United States and Reasons for Clinic Choice*, 28 J. Women's Health 1623, 1625 (2019), https://pubmed.ncbi.nlm.nih.gov/31282804/.

[35] Jonathan M. Bearak et al., *Disparities and Change Over Time in Distance Women Would Need to Travel to Have an Abortion in the USA: A Spatial Analysis*, Lancet Pub. Health e493, e495–96 (2017), https://www.thelancet.come/action/showPDF?pii=S2468-2667%2817%2930158-5 (in six states, a majority of women of reproductive age live more than 50 miles away from the nearest abortion provider, including two states where a majority live more than 150 miles from the nearest provider).

[36] Alice Cartwright et al., *Identifying National Availability of Abortion Care and Distance from Major US Cities: Systematic Online Search*, 20 J. Med. Internet Res. 7 (2018), https://www.jmir.org/2018/5/e186/.

[37] Jenna Jerman et al., Guttmacher Inst., *Characteristics of U.S. Abortion Patients in 2014 and Changes Since 2008* 1, 7 (May 2016), https://www.guttmacher.org/report/characteristics-us-abortion-patients-2014.

[38] *Id.* at 1, 5; *Abortion Surveillance — United States, 2018*, Ctrs. for Disease Control & Prevention [hereinafter *CDC Abortion Surveillance*], at Table 5, https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down (last updated Nov. 7, 2020).

[39] Jerman et al., *supra* n.37, at 1, 7; *CDC Abortion Surveillance* at Table 7, https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7_down.

[40] Jill Barr-Walker et al., *Experience of Women Who Travel for Abortion: A Mixed Methods Systematic Review*, PLOS ONE 14(4), at 2 (2019), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0209991; Daniel Grossman et al., *Change in Distance to Nearest Facility and Abortion in Texas, 2012 to 2014*, 317 JAMA Network 437, 437–38 (2017), http://sites.utexas.edu/txpep/files/2017/10/Grossman-et-al-HB2-Change-in-Distance-Abortion-JAMA-2017.pdf (in Texas, when the distance to the nearest abortion clinic increased by 25–49 miles, abortions decreased 25.3%; when the change was 50–99 miles, abortions decreased by 35.7%; and when the change was 100 miles or more, abortions decreased by 50.3%); Sharon A. Dobie et al., *Abortion Services in Rural Washington State, 1983–1984 to 1993–1994: Availability and Outcomes*, 31 Fam. Plan. Persp. 241, 241–44 (1999), https://www.guttmacher.org/sites/default/files/article_files/3124199.pdf (in Washington, when a decline in the number of abortion providers led to a 12 mile increase in travel distance for rural women, the abortion rate among that population decreased by 27%); Robert W. Brown et al., *Provider Availability, Race, and Abortion Demand*, 67 Southern Eco. J. 656, 658 (2001) (in Texas, an increase of 10% in the travel distance from a woman's county to the nearest city with an abortion provider was associated with a 2.3% decline in the abortion rate for white women, 2.7% for African-American women, and 5.0% for Hispanic women); James D. Shelton et al., *Abortion Utilization: Does Travel Distance Matter?*, 8 Fam. Plan. Persp. 260, 260–62 (1976), https://jstor.org/stable/pdf/2134397.pdf?seq=1#page_scan_tab_contents (in Georgia, for every 10 miles of distance from the major abortion providers in Atlanta, the number of abortions declined by 6.7 per 1,000 live births); Alison H. Norris et al., *Abortion Access in Ohio's Changing Legislative Context, 2010–2018*, 110 Am. J. Pub Health 1228, 1232 (2020), https://pubmed.ncbi.nlm.nih.gov/32437269/ (abortion rate in rural counties disproportionately affected by clinic closures decreased more than 30% over study period); Ushma D. Upadhyay et al., *Denial of Abortion Because of Provider Gestational Age Limits in the United States*, Am. J. Pub. Health 1687, 1689 (2014), https://doi.org/10.2105/AJPH.2013.301378 (finding that 58.3% of patients turned away because they were beyond the abortion clinic's limit and 67% arriving just before the limit attributed their delay to "travel and procedure costs" and 29.8% cited "not knowing how to get to a provider"; for first trimester patients, travel and procedure cost was the second-most cited reason for delay).

[41] 21 U.S.C. 355-1(f)(2)(C)(ii).

[42] Daniels et al., *supra* n.29.

APPENDIX

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EXHIBIT 1

Declaration of Graham T. Chelius, M.D.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

vs.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]

DECLARATION OF GRAHAM T. CHELIUS, M.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

Graham T. Chelius, M.D., declares and states as follows:

1. I make this declaration based on my own personal knowledge and if called to testify I could and would do so competently as follows.

2. I am a plaintiff in the above-captioned litigation, which challenges the U.S. Food and Drug Administration's Risk Evaluation and Mitigation Strategy ("REMS") for Mifeprex. I provide this declaration in support of that litigation. I do so in my individual capacity, and not on behalf of any entity with which I am associated or where I practice, including my employer, Hawaii Health Systems Corporation.

3. I am a board-certified Family Medicine physician based on the island of Kaua'i in Hawai'i. I practice medicine at Kauai Veterans Memorial Hospital ("Kauai Veterans") and its associated clinics, West Kauai Clinics. Kauai Veterans is located on the western side of the island in the town of Waimea, Kaua'i. Kauai Veterans currently employs about 275 people.

4. I am currently the Chief of Staff at Kauai Veterans, a position I have held since February 2018. Immediately before that, and after serving for several years as a board member, I served as the Chief Medical Officer for the Hawaii Health Systems Corporation's Kaua'i Region (which, in addition to Kauai Veterans, included Samuel Mahelona Memorial Hospital, on the eastern side of the

island in Kapa‘a, Kaua‘i), but resigned from that position in December 2017 in favor of this new opportunity as Chief of Staff. In my role as Chief Medical Officer, I was primarily responsible for managing the relationship between Hawaii Health Systems Corporation and the physicians who serve the Kaua‘i region, including participating in contract negotiations, overseeing physician staffing assignments, and responding to any complaints brought against physicians by both patients and staff. As Chief of Staff, I have very similar responsibilities, but rather than acting as a representative of the administration I am an elected representative of the physicians who form the medical staff. Both my current and former positions require that I be involved in resolving most conflicts that arise among the small clinical team at Kauai Veterans.

5. I received my medical degree from the University of Wisconsin in 2001, and completed my residency in Family Medicine at North Colorado Medical Center. Since January 2009, I have been practicing medicine in Hawai‘i at Kauai Veterans.

6. In my current role as Chief of Staff, I continue to treat patients. Within my specialty of Family Medicine, I focus in particular on women’s health, including obstetrics, and on chemical dependency treatment.

7. During the twelve years that I have been practicing medicine in Hawai‘i, I would estimate that I have cared for more than 2,750 pregnant patients

and delivered over 1,100 babies on the island of Kaua‘i. While many of my patients have much-wanted pregnancies, a substantial percentage choose to end their pregnancies, and come to me seeking abortion care. Most of these patients are medically eligible for the FDA-approved medication abortion regimen: Mifeprex followed by the drug misoprostol.

8. However, I am unable to prescribe Mifeprex to patients who need this medication because, as detailed below, complying with the requirements in the REMS that I procure, stock, and dispense Mifeprex at my health care facility—rather than issuing a prescription, from the privacy of my office, for my patient to fill at a pharmacy—would damage my professional standing locally, disrupt the workplace dynamics I am responsible for maintaining, interfere with my ability to continue to serve the many patients I now serve, and jeopardize my patients' confidentiality. The Mifeprex REMS deters clinicians and harms patients by imposing unique, unnecessary, and onerous requirements on their care. Put plainly, the REMS impedes my and other clinicians' ability to safely and appropriately care for our abortion and miscarriage patients as we would patients seeking any other service.

9. The distribution restriction substantially interferes with my ability to practice medicine in accordance with my professional judgment. Because of the Mifeprex REMS, I am unable to provide medication abortions to my patients, even

in situations when my best medical judgment would strongly counsel in favor of providing this care.

10. There is only a narrow window in which a patient can take the Mifeprex-misoprostol regimen for early pregnancy termination: this method has been approved by FDA only for the first ten weeks of pregnancy, and that is the period during which clinicians generally prescribe it. But patients cannot know they are pregnant until four weeks, and many patients do not realize they are pregnant until their sixth to eighth week. By the time a patient sees me, they typically have only a few weeks—indeed, often only a few days—in which to take the medications. If they cannot access Mifeprex within the window of availability, the only option is a surgical abortion. Nevertheless, because of the REMS, I am unable to provide medication abortion care in these time-sensitive situations.

11. There are no abortion providers on Kaua‘i, a federally designated "medically underserved area." The closest provider of abortion services is on O‘ahu, which can be reached only by airplane. I have seen the anxiety and confusion in my patients' eyes when I tell them that they have to fly to O‘ahu to obtain an abortion. I have heard them describe their frustration, anger, and heartbreak. For some patients—many of whom are already experiencing significant anxiety as a result of the unwanted pregnancy, and some of whom are also struggling with the challenges and trauma of poverty, drug addiction,

joblessness, and/or domestic violence—this news is simply devastating.

12. Traveling to O‘ahu for a surgical abortion costs my patients money and time, and causes them stress. Many are forced to make significant personal and financial sacrifices in order to get the health care they need. They must find the money to pay, or if possible make arrangements for insurance to pay, for the costs of transportation to and from the airports on both islands, and for the flights themselves. They must arrange to take time off from work or school, and arrange for child care if they have children, which most do. If a loved one is accompanying them to O‘ahu for support, that person must bear these costs as well. This travel and related logistics also impose significant psychological and emotional strain on many of my patients, and in my experience can be especially hard on young women, women struggling with substance abuse, women for whom English is not their first language, and women who are homeless.

13. Raising the money and making arrangements to travel is often time-consuming. Given the circumstances of my patients’ lives, it is not uncommon for it to take several weeks, a month, or longer. Indeed, even for those of my patients fortunate enough to have insurance coverage for the abortion procedure and the travel to obtain it (though, of course, still not for child care, missed work, or food away from home), it typically takes one to two weeks just for the paperwork to be approved. As previously noted, delays often mean that patients are no longer

eligible for medication abortion at all, and instead must have a surgical procedure. Moreover, while abortion is very safe, the risks increase as pregnancy advances. And, on top of that, patients whose abortions are delayed also face health risks associated with continuing a pregnancy for additional days, weeks, or months. For such patients, delaying their abortion means they are sicker, longer.

14. I recall one patient whose experience powerfully illustrates many of the harms caused and burdens created by the REMS. She is a woman whom I had been treating for substance use disorder and who had previously seen us for obstetrical care for her first child. She came to my office seeking an abortion prior to 10 weeks of pregnancy. After evaluating her, I concurred that a medication abortion was an appropriate treatment, that she could utilize the Mifeprex-misoprostol regimen, and that she should do so without delay. I wanted to—and would have—provided her with the medication abortion she desired if I could have written a prescription for Mifeprex for her to fill at a pharmacy. But, because of the REMS, I could not provide that care to my patient. Instead, she was forced to travel to O‘ahu.

15. Because of the complications in this woman’s life, by the time she was finally able to make the journey to O‘ahu, more than six weeks had passed. At that point, she had to have a two-day dilation and evacuation (“D&E”) abortion instead of the medication abortion she had wanted. Not only is D&E a significantly

more complex and invasive procedure, but it also required her to bear the costs of staying on O‘ahu—in a hotel, away from her home and her family—overnight. This was utterly unaffordable for her. Indeed, I understand that she called her sister on the day of her first appointment to tell her that she was on O‘ahu for an abortion and had only $20 in her pocket. Her sister jumped on the plane to help my patient find lodging and provide her with emotional support during the procedure—which of course meant that my patient’s sister also had to bear the costs of a round-trip flight, hotel, and food during her stay. Fortunately, her sister managed to drop everything and come to her aid, but otherwise I don’t know how she would have managed to get to and from her appointments or where she would have stayed overnight.

16. I still feel frustrated and upset that my patient and her family had to bear the emotional trauma, financial burdens, and medical risks of this experience. And she is far from the only patient I have had who was eligible for medication abortion at the time I saw her, but ultimately had to not only fly to O‘ahu to get the care they needed, but by the time they did so were too late for a medication abortion and had to have a procedure instead. Again, none of this would be necessary if I could have simply written this patient, and other patients like her, a prescription for Mifeprex when she was in my office early in her pregnancy.

17. While that patient *was* ultimately able to get an abortion—not all of my patients are. In some cases, the travel burdens created by the Mifeprex REMS are simply untenable, and my patients end up carrying pregnancies to term and having children against their will. For instance, one patient who struggles with chemical dependency never was able to get to O‘ahu, despite her expressed desire for an abortion and despite extensive assistance with the travel arrangements. As a result, she was forced to carry the pregnancy to term (and her child was exposed to drugs throughout the entire pregnancy). I have continued to care for such patients through the course of their pregnancies and beyond, and have seen firsthand the emotional, physical, and financial burdens that an unwanted pregnancy can cause.

18. Sadly, the situation is even worse for women who live on Ni‘ihau, which is a sparsely populated island just west of Kaua‘i. There are no paved roads, and no cell coverage—let alone health care—on Ni‘ihau. Because of the lack of access to reproductive health care on-island, women on Ni‘ihau have to schedule transportation by boat to Kaua‘i just to see a doctor. My hospital delivers virtually all the babies for pregnant women on Ni‘ihau. If a woman on Ni‘ihau wants to terminate her pregnancy, the obstacles are even greater for her than for a woman on Kaua‘i. But if the REMS did not exist, she could simply go to Kaua‘i to obtain Mifeprex the same day, instead of going to Kaua‘i only to then get referred to an O‘ahu-based abortion provider and facing all the associated obstacles. I mention

Ni‘ihau just to show how burdens can aggregate and compound into an entirely insurmountable barrier to accessing safe abortion care.

19. I became a doctor to make my patients’ lives easier, less painful, and more fulfilling. But, because of the REMS, I must watch them suffer medical, emotional, and financial burdens when I cannot provide them with the abortion care that they desire. In addition, as a physician, I am concerned about continuity of care—yet the restrictions imposed by the Mifeprex REMS mean that I must needlessly hand off my patients to someone else for care, breaking that continuity for absolutely no medical reason. While I am confident that the providers to whom I refer my patients in O‘ahu provide high-quality care, it pains me to have to turn my patients away and send them off island to get care they need and that I am perfectly competent to provide. The Mifeprex REMS thus prevents me from providing uninterrupted, comprehensive primary health care to my patients, as I strive to do whenever possible. It violates my fundamental beliefs as a health care provider to have to deny a patient’s request for time-sensitive, medically indicated care only because of medically unjustified restrictions like the Mifeprex REMS.

20. For the past several years, some of my patients have been able to avoid most of these burdens by participating in the Telemedicine Abortion Study (“TelAbortion”), which is run through the University of Hawai‘i. This study—which I understand operates as a temporary waiver of the REMS—allows certain

qualifying patients to receive Mifeprex by overnight mail from the study's principal investigators on O'ahu without having to fly to that island for care. Recognizing how difficult the journey to O'ahu is for many of my patients, wherever possible, I have assisted them in participating in the study. I believe this model of care delivery—mailing Mifeprex following a telemedicine visit—is safe and effective and a valuable option for my patients.

21. But the TelAbortion study's process carries its own burdens and complexities, and therefore excludes the most vulnerable, highest-risk patients. The cost of participation in TelAbortion presents the first hurdle. While the State of Hawai'i generally covers the cost of abortion services through its Medicaid program, it does not cover the cost of Mifeprex obtained through the TelAbortion study. Thus, Medicaid enrollees must pay out-of-pocket for Mifeprex provided through the study. This effectively excludes or deters many lower-income patients from participating.

22. The logistics are another hurdle. In most cases, the study protocols require that a participating patient first have a blood test and ultrasound performed, and then mail, fax, or email the results to a physician at the University of Hawai'i. Then, that physician must connect with the patient by secure videoconference at a set appointment time. Some of my patients—including some who are homeless, poor, or live in extremely remote parts of Kaua'i—do not have reliable internet or

cell phone service, access to technology with secure videoconferencing capability, or the ability to use this technology in a private space where they can speak confidentially. In such cases, I often have to step in to help them. On several occasions, I have stayed late at my office to let a patient use my computer to participate in the study, but this is not always possible: my patients' schedule, my schedule, and the schedule of the physicians on O'ahu do not always align, and certainly do not always align before the patient's window for a medication abortion closes. Helping my patients participate in the TelAbortion study has taken, and continues to take, many hours of my time—and even so, some of my patients still cannot successfully use it.

23. A third hurdle is that participating patients must have a physical address to which a package can be securely and confidentially mailed. But my patients who are homeless do not have such a safe address. So the study also cannot provide relief to such patients.

24. For all patients, even if they can gather the resources to participate in TelAbortion, the processes and requirements of participating in a research study delay care. I have on numerous occasions seen patients who were still within the window for a medication abortion, but did not have enough time to access it through the study.

25. Critically, I understand that the TelAbortion study is only temporary. When it ends, it will no longer exist as an option for me and my patients.

26. The harms and burdens I have described that both my patients and I are experiencing flow directly from my inability to issue a prescription for Mifeprex to be filled at a pharmacy or by mail order as I can do with countless other equally or less safe drugs. Most of these harms and burdens would be entirely eliminated, or substantially reduced, if the REMS were eliminated.

27. In addition, the REMS imposes a broader set of harms by deterring and blocking qualified clinicians from becoming medication abortion providers through its unique and unnecessary barriers. First, in order to comply with the requirement in the REMS that I procure, stock, and dispense Mifeprex at my medical facility, I would have to risk serious damage to my professional standing in my workplace and to my respected role in the local community. Abortion is an issue about which people hold very strong views, and some of my colleagues and staff members strongly oppose it. In my tight-knit workplace, attempting to establish a policy for procuring, stocking, and dispensing Mifeprex at our facility would create internal conflict, undermining the team cohesion that I am responsible for developing and maintaining as Chief of Staff. It would also jeopardize my ability to continue in that elected position, threaten initiatives I am undertaking to improve care within our hospital system, and reduce the time I have

to treat patients. I cannot afford these personal and professional risks.

28. To be clear, many of my colleagues and staff already know that I provide abortion referrals. I know that some staff oppose even this; some have directly expressed such views to me. But if I were to comply with the Mifeprex REMS, I would be doing more than just supporting access to abortion in my *individual* professional capacity—I would also have to involve, and win the approval of, multiple colleagues and staff members in the process of procuring, stocking, dispensing, and billing for Mifeprex within our health care facility. Asking or demanding that my colleagues who have deeply held views against abortion participate or assist in providing abortions would cause significant conflict among my staff—conflict that, as Chief of Staff, I would also be required to manage, if possible. The negative consequences for my professional standing and for carefully nurtured workplace dynamics, which benefit all of our patients, deter me from attempting to comply with the Mifeprex REMS.

29. Relatedly, I also have had serious personal safety concerns about the requirement in the REMS that I register with the drug manufacturer and drug distribution company as an abortion provider. I understand that they must keep confidential the list of clinicians registered to prescribe Mifeprex. But particularly in light of the many recent health care hacking incidents, I have been concerned about being inadvertently or maliciously exposed as an abortion provider, and the

resulting likelihood of public backlash to me and my family.

30. Of course, my name is now public in the context of this litigation, and my experience since filing this lawsuit has validated my earlier concerns. Since the lawsuit was filed, I have received numerous phone calls and letters from strangers relating to this litigation. Many of those communications were positive and supportive. But a few were negative and concerning. Based on security consultations, I now carefully examine envelopes for toxic material, and have tried to remember to only open packages that I have been expecting. We also installed a security system at our house. In a country where abortion clinic shootings are commonplace and abortion providers have been assassinated, I have feared risking my and my family's safety by following through with what the Mifeprex REMS requires.

31. I ultimately made the difficult choice to publicize my desire to provide abortion care through this lawsuit, because I believe this case has the potential to expand access to medication abortion for patients all across the country. My family and I felt that this goal was worth the risk to our safety and privacy. But we did not make that choice lightly, and I expect that I am not the only physician who has found the REMS requirement that I add my name to a list of all medication abortion providers in the country a serious deterrent to providing this care.

32. I am also concerned that compliance with the Mifeprex REMS would jeopardize my patients' privacy. By requiring that my facility be responsible for the purchasing, stocking, dispensing, and billing of Mifeprex—discrete responsibilities held by discrete members of our staff—the REMS injects many more people into the abortion care process. This raises real confidentiality concerns in the small-town community in which I practice. Everybody knows you and you know everybody in Waimea, a town of fewer than 2,000 people on an island of just over 65,000. In fact, it is not uncommon for members of my staff to bump into my patients at the grocery store, gym, or on the street. For myself, going to either of the two grocery stores in Waimea is a social event due to the fact that I will certainly know someone either working or shopping at the store.

33. Additionally, many members of the community have a family member, friend, or neighbor employed at Kauai Veterans, and, as a result, members of our community are sometimes nervous about seeking intimate medical care from us out of fear for their confidentiality. Certain elements of a person's medical history (history of abortion, sexually transmitted diseases such as HIV or gonorrhea, a history of rape, struggles with substance use disorder) are closely guarded by patients due to real or perceived stigma from those in the general population and medical providers.

34. For instance, I have a patient who, while pregnant, asked that a specific doctor not be involved in her care because she was afraid that the provider might divulge her medical history to family members of the doctor whom the patient also knew. Fortunately, I was able to sufficiently reassure this patient that I trust this physician to respect her confidentiality, which resulted in this patient continuing to receive care from us. But there is no doubt that, in our community, patients struggle with the decision of whether to get adequate medical care due to concerns about their confidentiality. And, indeed, it would be entirely reasonable for a patient to fear for the privacy of her abortion decision if she happens to know, for instance, some of the numerous people who may be involved with the billing, ordering, recording, and physical dispensing of medication at our facility (which, again, is a perfectly plausible scenario in our small town).

35. By contrast, if the Mifeprex REMS did not exist, I would be able to write a prescription for Mifeprex for my patient without needing to let anyone else know about the prescription except, at most, the patient's nurse, a medical records clerk, and the patient's trusted pharmacist (or a pharmacy on the other side of the island, or a mail-order pharmacy, if that is the patient's preference). The risk to my patients' confidentiality is thus substantially higher under the Mifeprex REMS.

36. The Mifeprex REMS also presents significant logistical hurdles. In order to stock and dispense Mifeprex onsite, I would need to first get a policy created for storing and dispensing the drug in the clinic, and then secure approval from the Pharmacy and Therapeutics committee at Kauai Veterans. I would also need to complete and submit all of the paperwork associated with becoming a certified prescriber under the Mifeprex REMS and setting up an account with the drug distribution company—a process that would take even more time and effort because the purchasing agreement would need to go through our contracting office, which has to follow burdensome state contracting guidelines and rules.

37. Of course, I am not now a certified prescriber (though I could easily satisfy the stated criteria for prescribing clinicians), because the certification requires me to provide a billing address and a shipping address where the Mifeprex can be sent to and then dispensed from—which, for the reasons I have stated, I am unable to do. And regardless of any certification requirement, I now provide and will always provide only medical care within the scope of practice for which I'm qualified. That is a well-recognized, basic standard of the medical profession.

38. As I have already noted, this approval process would be extremely challenging in the tense political climate surrounding abortion at my hospital, and it would almost certainly be subject to interference by colleagues and others who vehemently oppose abortion and therefore would object to a decision to stock

Mifeprex in our hospital system. As Chief of Staff tasked with maintaining good working relationships in my hospital, I find these risks unacceptable. They would not only interfere with my supervisory role, and the long-term positive changes for overall patient care that I am attempting to accomplish in that role, but also take valuable time away from my own practice.

39. In addition, I understand that the Mifeprex REMS would also require me to provide my patients with, and discuss and sign, a "Patient Agreement Form" describing the proper usage of, and risks associated with, Mifeprex as of March 2016. This special form requirement is unnecessary and singles out abortion in a manner that other medications, even much less safe medications, are not.

40. Informed consent counseling is a bedrock of medical care, taught as a core skill in medical school and reinforced by the American Medical Association's Code of Medical Ethics. I do not need any special requirement or form to ensure that I provide every patient with informed consent counseling, including discussion of proper usage and risks and what to do in the event that they need follow-up or emergency care. In fact, much less safe medications that I use in my chemical dependency practice, such as Sublocade®, which are controlled substances and are very high risk for patients, do not require any such "patient agreement form." Nor do the many other medications that I prescribe, that patients fill at a pharmacy, and that they take at home.

41. The bottom line is that, because of the REMS, I have been unable to provide my patients with essential health care that they need and that I am fully capable of providing. The REMS delays care, and forces patients to jump through hoops that are unnecessary, stigmatizing, and confusing. For some patients, the Mifeprex REMS makes abortion beyond reach. I greatly hope that Plaintiffs' motion for summary judgment once and for all lifts the unjustified REMS requirements from this safe, important drug, so that many other clinicians and I can provide it via prescription to our patients who need it.

42. I learned on April 13, 2021, that FDA has suspended the in-person dispensing requirement and authorized use of a mail-order pharmacy for providing patients with Mifeprex during the COVID-19 Public Health Emergency. I am exploring whether it will be possible for me to prescribe through a mail-order pharmacy under the special "supervision" requirement still imposed by FDA, and what kinds of contracts and/or billing practices may be necessary under FDA's non-enforcement guidance (which, of course, continues to treat Mifeprex differently than virtually all other drugs). I understand further that, even if I am able to take advantage of this in the short-term, this temporary allowance expires when the public health emergency ends. In short, there is an urgent need for

permanent relief through this litigation.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on 4/14/, 2021

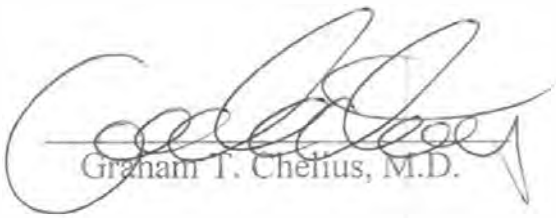

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EXHIBIT 2

Declaration of Julie Amaon, M.D.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

vs.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]

DECLARATION OF JULIE AMAON, M.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

Julie Amaon, M.D., declares and states as follows:

1. I make this declaration based on my own personal knowledge. If called to testify, I could and would do so competently as follows.

2. I am a board-certified family physician, licensed to practice in Minnesota, Texas, and Montana. I am trained to provide the full scope of family medicine with a focus on reproductive health care, including abortion.

3. Since July 1, 2020, I have been the Medical Director of Just The Pill, an organization founded in April of 2020 to improve access to sexual and reproductive health care for patients in rural Minnesota. To my knowledge, Just the Pill is the only mobile health center offering abortion care in the United States.

4. As a part of my practice, I prescribe mifepristone (brand name Mifeprex®) to patients seeking medication abortion. Because of restrictions imposed under the Food and Drug Administration ("FDA") Risk Evaluation and Mitigation Strategy ("REMS") for mifepristone, I cannot simply write a prescription for mifepristone for my patients to fill at a local or mail-order pharmacy, as they would for any other medication.

5. I can and do provide all counseling and assessment for eligible medication abortion patients in a telehealth visit, which FDA permits. FDA also permits my patients to take the medication at a location of their choice. But under the REMS, my patients have to travel in person to pick up their medication—a trip

that, for patients in rural Minnesota, can mean hours of travel each way and time away from family, and jobs. The challenge of arranging for lengthy travel and time away is often hugely burdensome for my patients, and, for some, means a delay of care beyond the point at which medication abortion is available to them or denial of access to abortion care altogether. In addition to these burdens, during the COVID-19 pandemic, the mifepristone REMS has subjected my patients and their families to needless risk of exposure to a deadly virus as they travel to pick up their medication.

6. I submit this declaration in support of the Plaintiffs' Motion for Summary Judgement in my individual capacity and not on behalf of Just The Pill or any other institution.

Limited Access to Abortion in Rural Minnesota

7. Minnesota's bricks-and-mortar abortion clinics are all located in three urban population centers: the Twin Cities, Duluth, and Rochester. According to the Guttmacher Institute in 2017, 61% of Minnesota women lived in a county lacking an abortion clinic.[1] Indeed, nearly half of the rural counties in Minnesota have no sexual or reproductive health clinics at all.[2]

[1] Jones RK, Witwer E & Jerman J, Guttmacher Inst. Abortion Incidence and Service Availability in the United States, 2017, at 17 (2019), https://www.guttmacher.org/report/abortion-incidence-service-availability-us-2017.

[2] Univ. of Minn. Healthy Youth Dev. Prevention Rsch. Ctr., 2019 Minnesota Adolescent Sexual

8. As a result, patients who reside in rural areas often must drive 3 or 4 hours *each* way to access abortion care, and sometimes longer in inclement weather during Minnesota's long winters. This travel requires patients to pay and arrange for transportation, time away from work, and child care, all of which can be costly and difficult. The expenses necessitated by this travel creates particularly weighty burdens for patients living with low incomes, which is the case for 75% of abortion patients.[3] As described below, for some patients the challenges they face in raising funds and arranging for travel and time away results in significant delays in their ability to access care and can prevent them from obtaining the abortion they seek.

COVID-19 and the Expansion of Telehealth Services

9. Just The Pill was established in the Spring of 2020, as the SARS-CoV-2 virus that causes COVID-19 spread through the United States, and access to abortion care in Minnesota became increasingly limited because of pandemic-related clinic closures and drastically reduced in-person care. At that time, the provision of health care in the United States was changing dramatically. Federal and state governments urged health care providers to use telemedicine to provide

Health Report 3 (2019), https://kstp.com/kstpImages/repository/cs/files/2019_ashr_final.pdf.

[3] Guttmacher Inst., Induced Abortion in the United States (2019), https://www.guttmacher.org/fact-sheet/induced-abortion-united-states#.

care whenever possible to maximize patient access to health care while minimizing the risk of viral transmission associated with travel to health care facilities during the pandemic.

10. At that time, I was working in a family medicine clinic, and like other physicians throughout the country, my practice transformed from an almost entirely in-person practice to one in which a broad range of primary care was offered by telehealth. However, because of the REMS, medication abortion patients were still required to travel in person to a health care facility to pick up their mifepristone. For patients in rural Minnesota, this meant continuing to travel long distances to access care. Just The Pill was created with the goal of helping such patients reduce the burdens and risks of travel by offering care from a mobile health clinic that could bring services closer to the patients.

11. In the summer of 2020, as Just The Pill was raising the funds to pay for its mobile health clinic, a federal district court in Maryland entered an injunction suspending the mifepristone REMS in-person requirements for the duration of the COVID-19 Public Health Emergency ("PHE").[4] This meant that mifepristone prescribers could mail or deliver mifepristone to patients or arrange to have the medication sent from a mail-order pharmacy.[5] As a result, Just The Pill

[4] *Am. Coll. of Obstetricians & Gynecologists v. FDA* [hereinafter "*ACOG v. FDA*"], 472 F.Supp.3d 183 (D. Md. 2020).

[5] *Id.*; *ACOG v. FDA*, Civ. No. TDA-20-1320, 2020 WL 8167535 (D. Md. Aug. 19, 2020).

pivoted from its plan to treat patients from a mobile health clinic and, in October of 2020, began offering medication abortion care via telehealth to eligible patients throughout Minnesota and delivering their medication directly to them through a mail-order pharmacy. However, in January of this year, the U.S. Supreme Court issued a stay of the injunction, reinstating the mifepristone REMS in-person requirements.[6]

12. From October of 2020 until the Supreme Court reinstated the mifepristone REMS in-person requirements, Just The Pill provided medication abortion by telemedicine with delivery from a mail-order pharmacy to nearly 100 patients in Minnesota. During this period, patients would schedule a telehealth appointment with me, where we would discuss the patient's medical history and symptoms to permit me to assess whether they were eligible for a fully remote medication abortion. If their medical history and symptoms were consistent with a fully remote medication abortion, I would provide comprehensive counseling, just as I would at an in-person visit. This included discussing the medication abortion process and the risks, benefits and alternatives to a medication abortion; reviewing FDA's Patient Agreement for mifepristone; informing the patient about our 24-hour-a-day phone line in the event that they had any questions after the appointment; reading the Minnesota state-mandated information about abortion;

[6] *ACOG v. FDA*, 141 S. Ct. 578 (2021).

and answering any questions they might have, ensuring that they had all the information they needed to make an informed decision about their care. After answering any additional questions, I would ask if they consented to a medication abortion, and if so, document that consent in their medical record. I would then *again* review the instructions for how and when to take their medication, what the follow-up process was, and what they should do if they experienced any of the (very rare) complications associated with mifepristone.

13. Following the telehealth visit, I would direct the mail-order pharmacy with which I have a contract for shipping and dispensing mifepristone to send the patient a package containing the medications (mifepristone, misoprostol, and, if requested, anti-nausea medication and ibuprofen for their comfort), written instructions, the mifepristone medication guide, and our 24-hour telephone number. We tracked shipments and confirmed delivery to patients from the mail-order pharmacy; the process was efficient and effective. As with the medication abortion itself, the medical follow-up for the vast majority of patients was also completed remotely, using telephone or audio-video communications and an at-home pregnancy test. None of the nearly 100 patients we treated through this process experienced a serious complication.

14. Being able to obtain their abortion medications from a mail-order pharmacy, without an unnecessary in-person trip to a health clinic, was a huge

relief for my patients. It enabled them to end their pregnancies earlier and more safely, without the need to travel long distances, arrange for child care, and take time away and lose pay from much needed jobs—and without the risk of viral exposure that jeopardized their health and lives and that of their families for no medical purpose. In a survey during part of this time in which 45 patients participated, 16 told us that, without the ability to have a telehealth visit and have their medication delivered directly to them, they would have had to delay care for "significantly more than 2 weeks," and 2 already knew they would not have been able to access abortion care at all and would have been forced to carry their unwanted pregnancies to term.

Burdens and Risk for Patients Following Supreme Court Stay

15. After the Supreme Court reinstated the mifepristone REMS in-person requirements, Just The Pill began providing care from a mobile health clinic at locations throughout the State to help patients access care. We did all evaluation and counseling with our patients via telemedicine, but we could no longer have their medication shipped to them; instead, they had to travel to where our mobile clinic was located on a given day.

16. We attempted to drive our mobile health clinic to locations that would be most helpful for our patients. These are largely places with communities facing the greatest barriers to traveling for care—such as communities with high

concentrations of migrant farm workers; areas with high poverty rates; and communities hardest hit by the COVID-19 pandemic, including those with large concentrations of Black, Indigenous, and people of color, and one particular community with a widespread outbreak of COVID-19 among workers at a meat-processing plant. However, we are a small operation, able to travel only a few days a week to a few different places in a very large state. Even with our atypical (and highly labor intensive) care delivery model, our patients continued to suffer significant burdens and risks as a result of the travel necessitated by the REMS.

17. For example, I recently treated a patient who lived in far northern Minnesota—on the Canadian border. Based on her medical history and symptoms, she was eligible for a fully remote medication abortion. I had conducted a telehealth visit with her, but, because of the REMS, she had to travel in person to pick up her medication. She scheduled her appointment on a day when we would be driving the mobile health clinic to our farthest north destination—approximately 4 hours northwest of Minneapolis. Even so, this meant that the patient had to travel 2 hours each way to us. She did not have a car and the only way for her to get to us was by cab, which cost approximately $300. When she arrived, she quickly got out of the cab, ran to the mobile clinic, and then immediately turned around to go home with her medication. Fortunately, we were able to raise private funds for this patient to get the care she needed. She told me that had assistance not been

available to pay for her to take a cab to our mobile clinic (or had Just The Pill's mobile clinic not been available), there is no way she could have afforded to get to clinic and she would have had to carry her pregnancy to term. But for the REMS, this patient could have received her medication without ever leaving her home.

18. We recently treated a patient who had 3 children, no car, and would have had to travel 3 hours round-trip to get to the nearest bricks-and-mortar clinic offering abortion care. We were able to treat her by telemedicine, but she had no one to care for her children and was unable to arrange for transportation to pick up her medication even from our mobile health center. In order to help this patient, we drove the mobile health clinic and parked it a block from her home so that she could walk to our mobile clinic. This was an extremely unusual situation; we simply could not do that for every patient. However, if we had not done so for this patient, she would not have been able to have the abortion she sought. But for the REMS in-person requirement, we could have had the medication sent directly to her following her telehealth visit.

19. Another patient with 4 or 5 children at home was trying to arrange to travel to our mobile health clinic to pick up her medication. This patient lived a 5-hour round-trip car ride from the nearest bricks-and-mortar clinic offering abortion care. She had a car, but it was not reliable, even for the 1-hour drive to our mobile clinic. We offered financial assistance for a cab, but this patient could not take

advantage of it, because she could not fit all of her children in the cab. Her spouse was a long-distance truck driver who was on the road most of the time, and, since the patient was new to the area, she did not have anyone she could turn to for child care assistance. To help this patient, we were able to drive the mobile health clinic to her town; however, this meant a delay of more than a week before she could obtain care. But for the REMS, we could have had her medication delivered directly to her home without such delay.

20. I have had numerous patients who have had to cancel appointments at the last minute because they can't get time off work, find child care, or forgo other obligations with which this travel interferes, or because their travel arrangements have fallen through. For some of these patients, when they tried to reschedule, we had to tell them that they were no longer eligible for a medication abortion because they were beyond 10 weeks in pregnancy. When that happens, we refer them to other abortion providers who offer in-clinic procedures, but, since there are so few abortion clinics in the state, this generally means even lengthier and more costly travel, and therefore more delay. Given the challenges that prevent such patients from accessing even our mobile clinic, I feel certain that some were never able to make the journey to a brick-and-mortar clinic in one of Minnesota's urban centers and therefore were forced to continue their pregnancies and have a child. But for

the REMS, these patients could obtain care without delay by telemedicine and home delivery of medication.

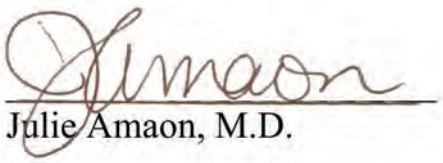
Barriers to Prescribing Mifepristone

21. Even though medication abortion could be safely provided in primary care and other health care settings throughout the state, the REMS requires health care providers to register as certified prescribers with the REMS program and stock mifepristone onsite for in-person dispensing. I have seen how these requirements prevent would-be mifepristone prescribers from providing this essential care to their patients. I know clinicians who would have prescribed mifepristone but were prevented from stocking and dispensing it onsite by others at the facilities in which they practice. For example, the family medicine clinic where I did my residency training was not permitted to stock mifepristone onsite because of opposition from someone at the institution. If it were not for the REMS, however, clinicians would have been able to send in mifepristone prescriptions to a pharmacy, as they do for virtually all other medications. Instead, because of the REMS, clinicians who practiced at the clinic could not provide mifepristone to their patients. The mifepristone REMS creates unnecessary barriers to the provision of care.

22. Earlier this week, FDA announced that it would suspend enforcement of the REMS in-person requirements during the COVID-19 PHE. This is

extremely good news for my patients, who now again have the opportunity to receive care by telehealth and have their medication delivered directly to them from a mail-order pharmacy. However, this non-enforcement policy is limited to the PHE: when the PHE ends, the REMS in-person requirements will again harm my patients as they have in the past.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on April 14, 2021.



Julie Amaon, M.D.

EXHIBIT 3

Declaration of Joey Banks, M.D.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

vs.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]

DECLARATION OF JOEY BANKS, M.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

Joey Banks, M.D. declares and states as follows:

1. I make this declaration based on my own personal knowledge. If called to testify, I could and would do so competently as follows.

2. I am a family medicine physician. I work at Blue Mountain Clinic in Missoula, Montana, where I have been providing care since 2011. I currently provide and train residents in reproductive health care, including abortion, at the Blue Mountain Clinic and also provide such care at a clinic in Tulsa, Oklahoma.

3. In addition, I serve as the Chief Medical Officer for Planned Parenthood of Montana, a position I have held since 2019. In this capacity, I supervise the medical staff at all Planned Parenthood sites statewide and also provide reproductive health care to patients.

4. In my practice I prescribe mifepristone (brand name Mifeprex®) to my patients both for pregnancy termination and in cases of pregnancy loss (where mifepristone assists in safely and efficiently completing the miscarriage). I have provided abortion and miscarriage care to patients for 20 years and, over the years, have provided such care to many people who lived in areas where care is difficult to obtain—including in Alaska, Maine, Montana, and, most recently, in Oklahoma.

5. I am a member of the National Abortion Federation, the American Academy of Family Physicians, and the Montana Academy of Family Physicians. I am also a member of the Society of Family Planning ("SFP"). I understand that SFP is a plaintiff in litigation challenging FDA's imposition of a Risk Evaluation and Mitigation Strategy ("REMS") for mifepristone, and write this declaration in support of SFP's Motion for Summary Judgment. I do so in my individual capacity and as an SFP member, and do not speak on behalf of Blue Mountain Clinic, Planned Parenthood, or any other institution.

6. Until a couple of years ago, Blue Mountain Clinic was the only clinic in Missoula where patients could access abortion care. The Blue Mountain Clinic is located near a perinatologist's office. A perinatologist is an obstetrician who specializes in maternal-fetal medicine and has special training in high-risk pregnancy care. Perinatologists sometimes use mifepristone to induce labor in late pregnancy.

7. The perinatologist near my clinic did not stock mifepristone, but occasionally wanted to administer it to his patients to induce labor in late pregnancy. Knowing that I stocked and provided mifepristone to my patients, in 2018 the perinatologist approached me about whether I would be amenable to his sending his patients to see me just to obtain the mifepristone, and then he would re-assume care after the patient left my clinic.

8. When I asked the perinatologist why he didn't stock mifepristone himself, he said it was because he was worried that by stocking mifepristone he would unwittingly be placed on a list of abortion providers. The perinatologist was aware of the history of violence and harassment by anti-abortion activists and was concerned that if the list of mifepristone prescribers required by the REMS were somehow made public, it would put him in danger.

9. The perinatologist was affiliated with and provides services at a local hospital in Missoula, Montana. When I asked why he didn't just ask the hospital to stock mifepristone in its formulary, he said that he did not want anyone in the hospital to presume he was pro-choice.

10. This is not the only instance in which I have encountered clinicians who are unwilling to stock mifepristone even though it would benefit their patients. For instance, since 2013, I have been providing reproductive health care training to family medicine residents at Blue Mountain Clinic. My training includes, among other things, medication abortion, procedural (sometimes called "surgical") abortion, and miscarriage management. For many

years, I have taught residents to treat patients seeking medication abortion with a regimen of 200mg of mifepristone followed by 800mg of misoprostol; and, since 2018, based on new, high-quality medical research, I also began teaching them this two-drug regimen for the medical management of miscarriages. Although both can be accomplished with misoprostol alone, evidence supports the two-drug regimen as the superior regimen.

11. On numerous occasions, I have been contacted by physicians I previously trained, telling me that the health care facility where they work does not stock mifepristone, and that they felt uncomfortable asking leadership at their health care facility to begin stocking mifepristone, or that they knew their clinic simply would not stock mifepristone. They all wanted to know whether they could still care for patients who sought a medication abortion or suffered a miscarriage, even without mifepristone. In light of these conversations, I now explain to the residents I train that if their health care facility does not stock mifepristone, they can consider prescribing misoprostol alone for either early abortion or miscarriage treatment, but that it is less effective and that the two-drug regimen, including mifepristone, is the superior regimen

12. In my experience, the mifepristone REMS is interfering with practitioners' provision of evidence-based medicine. Some clinicians fear professional repercussions if they try to persuade their colleagues to stock and dispense mifepristone onsite. And some are so concerned about the stigma and threat of violence surrounding the provision of abortion that they are unwilling to register their names and addresses with the mifepristone distributer, as required by the REMS. The prospect of this "abortion provider list" being leaked to the public is enough to prevent clinicians from providing what they deem the best medicine for their patients.

13. In sum, the mifepristone REMS prevents clinicians from providing solid evidence-based medicine due to the stigma and fear associated with having to register with the

drug manufacturer and stock the medication onsite.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on April 12, 2021.

Joey Banks, M.D.

EXHIBIT 4

Declaration of Jared Garrison-Jakel, M.D.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

vs.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]

DECLARATION OF JARED GARRISON-JAKEL, M.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

Jared Garrison-Jakel, M.D., declares and states as follows:

1. I make this declaration based on my own personal knowledge. If called to testify, I could and would do so competently as follows.

2. I am a board-certified family medicine and addiction medicine doctor in Guerneville, California, and a member of the California Academy of Family Physicians ("CAFP"). I understand that CAFP is a plaintiff in this litigation challenging the U.S. Food and Drug Administration's imposition of a Risk Evaluation and Mitigation Strategy ("REMS") for Mifeprex, and write in support of that litigation. The Mifeprex REMS causes injury to me and my patients. But for the REMS, I could and would provide Mifeprex to my patients.

3. I received my undergraduate degree from Pomona College in 2005, a Master's in Public Health from the University of California Berkeley in 2009, and my medical degree from the University of California Irvine School of Medicine in 2010. I subsequently completed an internship and residency in family medicine at Sutter Medical Center of Santa Rosa in California.

4. I am trained in both medication and surgical abortion and provided those services while in my residency at Sutter Medical Center of Santa Rosa.

5. Since 2013, I have practiced at Russian River Health Center in Guerneville, California ("Russian River"). I submit this declaration in my individual capacity and— besides CAFP—not on behalf of any institution with

which I am associated, including the health center.

6. Russian River is a federally qualified health center ("FQHC"). FQHCs offer primary health care services to low-income populations in medically underserved areas. Guerneville, where Russian River is located, is an economically depressed city with virtually no other health care facilities. Our health center is located about 30 minutes away from any other doctor's office.

7. Many of my patients have little access to transportation outside of the community where Russian River is located. This lack of transportation makes it difficult to access even urgent health care services. For example, I treated one patient who had a terrible cut in her hand—the laceration reached the tendon. I told this patient that she needed to see a hand surgeon due to the severity of the laceration, but the patient explained that such travel would be impossible for her. She told me, "Doc, either you fix it now or no one's fixing it."

8. As explained below, because of the REMS, medication abortion is not available in the health center where I work. As a result, I have had to turn away patients who need abortion care. The closest clinic that offers abortion services is a one-hour round-trip from our health center. Traveling such a distance is a significant impediment for the populations I serve, who generally struggle to afford and arrange for things like transportation and child care. And, making this journey may very well also require my patients to miss work, and therefore lose wages—

that is, if they can get time off work at all; at the low-wage jobs where my patients typically work, there is often no paid leave. The reality is that it can be difficult or impossible for my patients to overcome all of these barriers.

9. I am medically qualified to provide Mifeprex to my patients who request a medication abortion. The only reason why I am not able to do so is because of the requirement that I stock and dispense Mifeprex on site.

10. I am aware that at least one of my colleagues, who holds a position of authority at our institution, is opposed to abortion and would not consent to Mifeprex being stocked and dispensed in our health center. (For the same reason, we cannot provide surgical abortion services here.) However, I am also aware that this colleague would not interfere with my writing a prescription for Mifeprex in the privacy of my office for a patient to fill at a pharmacy—and there are two pharmacies very close to the health center where I work; one is only a block away. But for the REMS, I could and would provide medication abortion care to my patients (and would do so in compliance with all federal segregation guidelines for FQHCs that provide abortion services).

11. Because of the REMS, I have been unable to treat my patients in accordance with my medical judgment. Multiple patients have come to me with unwanted pregnancies at less than ten weeks, who requested—and were eligible for—medication abortions. However, because of the REMS, I had to deny them

this care—delaying their abortion, to the extent that they could obtain the abortion at all. Indeed, I am always reluctant to refer a patient to another health care facility, whether for abortion or any other medical service; given the financial challenges that my patients almost uniformly face, which are often compounded by other barriers and stressors (such as mental health disorders, substance use disorders, or homelessness), such a referral usually means that they will be significantly delayed in accessing medical care, or not obtain it at all.

12. There are three central concerns with delaying abortion care. First, if a patient is delayed past ten weeks of pregnancy, she typically will no longer be able to obtain a medication abortion and will instead need to have an in-office clinical procedure, which may be an inferior option given her circumstances. Second, while abortion is extremely safe, and far safer than remaining pregnant and carrying to term, the risk of complications increases as the pregnancy progresses. I can recall at least one patient who came to me at a point in pregnancy when she was still eligible for a medication abortion but, because I could not write her a prescription for Mifeprex, ended up having a more invasive and time-consuming second-trimester dilation and evacuation abortion procedure over a month later. Third, delaying a patient's abortion means that the patient stays pregnant longer, and thus must incur the serious risks and discomforts associated with pregnancy for longer.

13. Moreover, because of the REMS, at least one of my patients was prevented from having a desired abortion at all. This patient had a history of sexual trauma and struggled with substance use disorders. She was extremely distressed to learn that she was pregnant, and presented to me seeking a medication abortion. To add to the complications of her situation, she did not feel that she could disclose her desire for an abortion to her partner. I initially referred her to the nearest clinic providing first-trimester abortion services, but she was unable to make the journey to that clinic for her appointment. I saw her again in her second trimester, when she reiterated that she did not want to carry the pregnancy to term. At that point, I referred her to the nearest provider of second-trimester abortions, which is approximately three hours round-trip from Guerneville. I know that the care team at that facility worked diligently to support her in accessing abortion care, including trying to arrange transportation for her. Nevertheless, because of the many challenges in her life, she missed multiple appointments there as well. This patient ultimately ended up carrying the pregnancy to term. I have grave concerns about how this unintended pregnancy has affected her life; when I'd seen her, she communicated that the pregnancy had worsened her suffering around her sexual trauma history and medication dependency. Moreover, this patient did not obtain adequate prenatal care during her first or second trimesters because this was not a pregnancy she had intended to carry to term. Needless to say, denying this patient

the care she so desperately wanted and needed was not in accordance with my best medical judgment.

14. In short, the Mifeprex REMS has prevented me from fulfilling my personal, professional, and ethical obligations to provide my patients with the medical care they need, which I am qualified to and would otherwise provide.

15. I am aware that the FDA just announced that, for the remainder of the COVID-19 Public Health Emergency, it is suspending enforcement of the requirement that patients obtain Mifeprex in person at a health center and instead allowing patients to obtain their medication by mail or from a mail-order pharmacy acting under the supervision of a certified REMS prescriber. Although this is an important step in the right direction, even under this short-term policy, the FDA continues to treat Mifeprex differently than any other drug I prescribe. I am working to understand what this "supervision" requirement entails (such as with regard to billing) and determine whether or not I will be able to take advantage of this temporary policy shift. Regardless, a permanent fix is essential to ensure that my patients can access medication abortion care without facing needless, and sometimes insurmountable, hurdles.

I declare under penalty of perjury that the foregoing is true and correct and that this declaration was executed on April 14th, 2021, in Guerneville, California.

Jared Garrison-Jakel, M.D.

EXHIBIT 5

Declaration of Erin King, M.D.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

vs.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]

DECLARATION OF ERIN KING, M.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

Erin King, M.D. declares and states as follows:

1. I make this declaration based on my own personal knowledge. If called to testify, I could and would do so competently as follows.

2. I am a board-certified Obstetrician Gynecologist ("Ob-Gyn") licensed to practice in Illinois and Missouri. I treat patients principally at a general Ob-Gyn practice in St. Louis, Missouri, and at the Hope Clinic for Women ("Hope Clinic") in Granite City, Illinois, where I also serve as the Executive Director. I provide patients with the full scope of obstetric and gynecological care, including abortion care.

3. I am a member of the American College of Obstetricians and Gynecologists, the National Abortion Federation, and the Society of Family Planning ("SFP"). I understand that SFP is a plaintiff in this litigation challenging the Risk Evaluation and Mitigation Strategy ("REMS") that the Food and Drug Administration ("FDA") imposes for mifepristone (brand name Mifeprex®). I write this declaration in support of Plaintiffs' Motion for Summary Judgment, on my own behalf, and not on behalf of Hope Clinic or any other institution.

4. I am a certified prescriber under FDA's mifepristone REMS. I prescribe mifepristone as part of a medication abortion regimen and for patients seeking medical management of miscarriage. I also provide training in medication abortion and other abortion and reproductive health care.

5. I am aware of clinicians who would prescribe mifepristone for medication abortion and miscarriage care for their patients if they could send in a prescription to a local or mail-order pharmacy as they do with nearly all other medication. However, the mifepristone REMS—which requires clinicians to register as certified prescribers and to stock and dispense mifepristone in their offices—has prevented them from using mifepristone in their patient care. Physicians I have trained have often told me that they are unable to find employment with practices that are willing to stock mifepristone and, as a result, were not able to provide medication abortion or miscarriage care using mifepristone to their patients, though they would have been able to provide this care if they could simply write a prescription.

6. The mifepristone REMS also imposes significant burdens on my patients. Because of the REMS, my patients whom I can evaluate and counsel via telemedicine have had to travel unnecessarily to my clinic for their medication. They have had to find and pay for transportation and child care and take time away from jobs that pay by the hour or day. This is particularly burdensome for my many patients who live with low incomes and have to travel long distances, from rural parts of southern Illinois, to get to my clinic. In addition, during the COVID-19 pandemic, the REMS has put them and their families at needless risk for contracting a deadly virus as they travel in person to pick up medication that they

could otherwise safely receive by mail at home.

7. Last year, a federal district court in Maryland issued an injunction suspending the mifepristone REMS in-person requirements for medication abortion for the duration of the COVID-19 federal Public Health Emergency ("PHE").[1] The injunction permitted me to contract with a mail-order pharmacy to ship mifepristone to my eligible patients. That meant that, for my medication abortion patients who did not require in-person assessment, I could provide all counseling and assessment in a telehealth visit and then have the medication delivered directly to them from the mail-order pharmacy.

8. On the day we began offering patients the option to receive their prescription through the mail-order pharmacy, I treated a patient who had had an appointment to come to the clinic for a medication abortion but had had to cancel because she could not get time away from work and could not find anyone to stay with her children. She told me that she would have had to forgo an abortion altogether if we had not been able to offer her a telemedicine visit and delivery of her medication, because she did not think she would ever be able to make the arrangements necessary to get to the clinic in person. But, because the REMS in-person requirements were enjoined, she was able to have a safe abortion from the

[1] *Am. Coll. of Obstetricians & Gynecologists v. FDA* [hereinafter "*ACOG v. FDA*"], 472 F.Supp.3d 183 (D.Md. 2020); *ACOG v. FDA*, Civ. No. TDA-20-1320, 2020 WL 8167535 (D.Md., Aug. 19, 2020).

safety and privacy of her own home.

9. Unfortunately, however, the U.S. Supreme Court entered a stay of the injunction, reinstating the in-person requirements.[2] As a result, for the past three months I have again been forced to require patients seeking medication abortion care to travel to the clinic to pick up their medication.

10. This requirement imposes substantial burdens on my patients. Since the Supreme Court reinstated the REMS in-person requirements, I have seen numerous patients who needed no in-person assessment but nevertheless had to travel multiple hours, each way, to come to my clinic to pick up their medication. These patients have had to bear the costs and burdens of arranging travel, time away from work, and child care, when they could just as safely have obtained their prescription by mail and avoided all of these burdens.

11. Needing to make these arrangements and raise funds for this travel has often delayed my patients' care—sometimes beyond the point when they can have a medication abortion. I recently saw a patient who wanted a medication abortion but was 13 weeks pregnant and therefore had to have an in-clinic procedure. She was very upset, explaining that she had rescheduled her appointment numerous times because she could not arrange for travel or find someone to take care of her children—and during the pandemic, she could not

[2] *ACOG v. FDA*, 141 S. Ct. 578 (2021).

bring her children with her to our clinic, because we do not allow anyone other than the patient to enter in order to mitigate viral spread. But for the mifepristone REMS, I could have treated this patient in a telemedicine visit and had her medication delivered to her at home while she was still eligible for a medication abortion. This patient is not alone; I see patients every week with one variation or another of this story.

12. I am able to provide care entirely by telehealth for a wide array of other medical needs. For instance, I regularly use telehealth to diagnose, treat, and counsel patients regarding urinary tract infections, vaginitis, rashes, and contraception needs. In my practice, we also conduct prenatal and post-partum visits remotely. We can even examine a patient's sutures and evaluate how well the patient is healing after surgery in a telehealth visit. I can just as safely and effectively evaluate and comprehensively counsel eligible medication abortion patients in a telehealth visit. However, because of the REMS, my patients who require mifepristone have had to suffer needless burdens and risks that my patients who can obtain care entirely by telehealth are able to avoid.

13. Earlier this week, FDA announced that it would suspend enforcement of the REMS in-person requirements during the COVID-19 PHE. I am very pleased that my patients receiving care by telehealth can now have their medication delivered directly to them from a mail-order pharmacy without the

costs, risks, and burdens of a needless in-person trip. However, when the PHE ends and this non-enforcement policy expires, the REMS in-person requirements will again impose substantial burdens on my patients.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on April 14, 2021.

Erin King, M.D.

EXHIBIT 6

Declaration of
Charisse M. Loder, M.D., M.SC.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

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Plaintiffs,

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XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]
DECLARATION OF CHARISSE M. LODER, M.D., M.SC., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

Charisse M. Loder, M.D., M.Sc., declares and states as follows:

1. I make this declaration based on my own personal knowledge. If called to testify, I could and would do so competently as follows.

2. I am an obstetrician-gynecologist trained in abortion care and a member of the Society of Family Planning ("SFP"). I am a Clinical Assistant Professor of Obstetrics and Gynecology at the University of Michigan Medical School. My practice is located at the Women's Clinic at Von Voigtlander Women's Hospital in Ann Arbor, Michigan. I have also practiced as an obstetrician-gynecologist at Planned Parenthood in Ann Arbor.

3. I received my undergraduate degree from Cornell University in 2003, and my medical degree from Pennsylvania State University in 2011. I did my residency in Obstetrics and Gynecology at the University of Rochester, where I served as Chief Resident, and then completed a fellowship in Family Planning and received a Master of Science degree in Health and Health Care Research at the University of Michigan.

4. In my current practice, I provide a range of obstetrics and gynecology care, and specialize in miscarriage management, complex contraception and sterilization, and abortion care.

5. I submit this declaration in support of Plaintiffs' Motion for Summary Judgment. I do so only in my individual capacity and as a member of SFP, not on behalf of any institution with which I am affiliated.

6. Mifeprex is an important drug for the provision of abortion and miscarriage care. I advocated to make this medication available within the Women's Clinic in order to offer our patients the best possible care at our own institution, without having to refer them elsewhere.

7. While I am currently able to prescribe mifepristone to my patients, attempting to bring the Women's Clinic at the University of Michigan into compliance with the mifepristone (brand name Mifeprex®) Risk Evaluation and Mitigation Strategy ("REMS") was an extremely complicated process that took five years (and a substantial investment of time, resources, and professional capital by me and other colleagues). During these five years, my colleagues and I were forced to refer patients who needed medication abortion care to other institutions. When patients are referred elsewhere for abortion care, many experience delays or are even prevented from accessing this time-sensitive care. We were also unable to offer Mifeprex for miscarriage and second-trimester abortion care, even though Mifeprex enhances the efficacy of those treatments. There is absolutely no medical reason for FDA to impose these barriers to patients obtaining this safe and effective medication.

8. My involvement in the process of trying to make Mifeprex available at the University of Michigan began when I arrived at the University six years ago, in 2015. But conversations surrounding Mifeprex at the University of Michigan began seven years ago, in 2014. As of 2014, the only patients who could access mifepristone through the University of Michigan were those seeking treatment for Cushing's syndrome: University clinicians were able to prescribe mifepristone under the brand name Korlym, and the patients filled those prescriptions through a mail-order pharmacy. However, patients in need of mifepristone under the brand name Mifeprex, for reproductive health care, could not access the medication through any University provider.

9. As a first step, I had to get approval to add Mifeprex to the University's drug formulary from the University's Pharmacy and Therapeutics Committee ("the Committee"), which is composed of pharmacists and physicians from a variety of clinical specialties. As discussed above, I was not the first physician to attempt to do so; in 2014, other physicians had participated in multiple meetings with the Committee during which they advocated for adding Mifeprex to the formulary. Ultimately, these conversations stalled because those physicians were unable to invest the immense amounts of time required to move this process forward.

10. Between 2015 and 2016, I participated in approximately four Committee meetings relating to Mifeprex. To assist in the Committee's evaluation of Mifeprex, the Committee asked me and my colleagues to provide literature on Mifeprex's safety and indications for use, which we did. These meetings were each about an hour long, and I individually spent at least 20 additional hours researching and preparing presentations about Mifeprex's safety and efficacy, as well as writing guidelines for its use.

11. Finally, in 2016, the Committee approved Mifeprex for the University formulary. None of this would have been necessary—the Committee would not have been involved at all—if we could simply issue our patients a prescription to fill at a pharmacy instead of having to stock and dispense Mifeprex onsite.

12. But getting Mifeprex on our hospital's formulary still did not mean that University of Michigan clinicians could start prescribing Mifeprex to patients. Placing a drug "on formulary" means that the drug is approved for safe use by the hospital. But, in order to make Mifeprex available "in clinic" for patients, the University of Michigan first had to order and stock this medication. And it took me *three* more years of advocacy to achieve this second step.

13. In 2018, a pharmacist in the gynecology department suggested that I form a task force to develop protocols for Mifeprex use in-clinic because the process had stalled out. I believe that my colleague suggested that I create such a

task force in order to alleviate concerns throughout the University about how to comply with the Mifeprex REMS and to accelerate the process of actually stocking and dispensing Mifeprex. I have never heard of such a task force being formed for the introduction of other drugs or devices into University practice. For example, we frequently integrate new intrauterine contraceptive devices (IUDs) into our practice, and have never had to develop protocols about how to prescribe them. But I believed that without a physician champion and a committee specifically focused on this issue, Mifeprex would never be made available in our clinic.

14. Accordingly, I organized and created a multidisciplinary task force to develop various protocols for ordering, stocking, prescribing, and dispensing Mifeprex at the Women's Clinic. This task force is made up of gynecology and family medicine physicians, nurses, clinic managers, pharmacists, and electronic medical record (EMR) specialists. The task force was charged with finalizing protocols to address how Mifeprex is ordered, administered, and stored, as well as addressing safety and reimbursement concerns surrounding the storage and dispensing of Mifeprex at our clinic. In a large health care institution like ours, where every organizational decision requires approval from multiple stakeholders, none of these decisions were simple.

15. I first convened this task force in October 2018, and the task force met every six weeks until Mifeprex was available in clinic. The task force met for

about an hour each time—and that is only the tip of the iceberg. Since October 2018, I have spent at least 80 hours of my time preparing for and/or completing follow-up work relating to task force meetings (such as preparing education materials for clinical staff), as well as participating in numerous *non*-task force meetings with stakeholders to discuss protocols to ensure compliance with the REMS as we integrate Mifeprex into clinical practice. For instance, I met with EMR representatives to propose edits to our electronic medical records in order to track Mifeprex administration in patient records. I attended separate meetings with the Women's Clinic manager, insurance verification team, and billing team related to the University's financial and reimbursement concerns around the dispensing of Mifeprex onsite. And I consulted on strategies to communicate guidelines for Mifeprex administration with staff, including developing REMS-compliant protocols for nurses who may want to "opt-out" of any involvement in the dispensing of Mifeprex. If not for the REMS, I would not have had to involve all of these other clinicians and stakeholders within the University and invest so many hours of my time and professional resources into developing system-wide protocols to integrate Mifeprex into hospital practice. I would simply have written my patients a prescription.

16. The Mifeprex REMS also requires that clinicians register with the drug's distributor in order to become a certified prescriber. As an initial matter, this

requirement is medically unnecessary: Mifeprex is a safe and straightforward medication; the clinical competencies necessary to safely prescribe it are very common; and in general, and as a legal and ethical matter, my colleagues and I do not prescribe any treatment unless it is within our competency to do so. But the prescriber certification requirement also posed numerous obstacles to the provision of Mifeprex at the University of Michigan.

17. First, task force members raised concerns that the University would face legal liability if clinicians who were not acting pursuant to a REMS prescriber agreement prescribed this drug. We spent many meetings discussing protocols to prevent violations of the REMS.

18. Second, members of the task force were concerned about how to store Mifeprex to ensure that only certified prescribers can access it. As a result, the task force spent numerous meetings discussing how to properly secure the Mifeprex stock with locks, and how to determine which clinicians have access to the locked area.

19. Third, because of the prescriber certification requirement, the University of Michigan must update its EMR system and pharmacy database each time a physician registers as a certified provider. These updates are costly and require staff time. These systems must be updated constantly to alleviate a concern that someone will prescribe Mifeprex in violation of the REMS.

20. These organizational concerns related to prescriber certification stem not from any mistrust of physicians, but from concerns about compliance with the REMS.

21. I would never have been able to provide mifepristone to my patients if it were not for the tenacious advocacy and time commitment my colleagues and I invested into this effort. As it was, for more than five years, the REMS prevented me and all of my colleagues from providing that care to our patients and necessitated that we refer patients outside of the University of Michigan system. I know that many of my colleagues have had the same experience, because over the years, I have frequently been contacted by colleagues inquiring whether they were permitted to prescribe Mifeprex to their patients, and I had to tell them that—because of the REMS—the answer was no.

22. And my situation at the University of Michigan is by no means unique. I am regularly contacted by clinicians at other academic medical centers who are seeking advice on how to navigate the REMS in order to stock and dispense Mifeprex at their institutions.

23. Clinicians outside the University of Michigan have also shared with me that they have not integrated Mifeprex into their practice because they fear that completing the REMS prescriber certification requirement would place them on a registry of abortion providers and thus make them targets of anti-abortion

harassment or violence. If clinicians could simply write a prescription for Mifeprex without this obstacle and the other obstacles the REMS imposes, I believe that many more clinicians, in a wider swath of our state, would do so.

24. While abortion care is extremely safe, the risks associated with abortion increase as pregnancy advances. Therefore, delaying a patient's abortion care increases the risks she faces.

25. This delay also pushes patients past the point at which a medication abortion, or any abortion care, is available to them at all. When I worked at Planned Parenthood, I often saw patients who had been referred there by their primary provider because their provider does not provide medication abortion care. But, because of the delay caused by this referral, by the time these patients got to Planned Parenthood, they were frequently too far along in their pregnancies to be eligible for a medication abortion—even though they preferred that option and that option would have been most clinically suitable for them. Because of this delay, these patients were only eligible for aspiration or dilation and evacuation ("D&E") abortion, in-clinic procedures that are significantly more expensive than medication abortion. And some of these patients could not afford these more expensive in-clinic procedures and ultimately were unable to get an abortion at all.

26. My patients at Planned Parenthood frequently told me about the burdens they faced traveling to us for care: paying for transportation, arranging

child care, taking time (often unpaid) off from work, and more. Some of these patients traveled great distances: there are very few abortion providers in Northern Michigan or in Michigan's Upper Peninsula, and many of our patients traveled more than one and a half hours, and up to 10 hours, to obtain abortion care. Many of these patients shared that they could not access abortion care in their local community.

27. In addition to being an important part of safe, effective early abortion care, Mifeprex has other clinical indications, such as in medical management of pregnancy loss (miscarriage) and labor induction abortions during the second trimester. In both of these clinical circumstances, pretreatment with mifepristone reduces the length of the treatment and, as a result, reduces the risk of complications.

28. At the University of Michigan, my colleagues and I care for patients undergoing second-trimester labor induction in cases of pregnancy loss, or where the patient seeks abortion because of a diagnosis of fetal anomalies or due to significant risk to maternal health or life. During this process the patient experiences all the pain and physical consequences of labor. Clinicians often prescribe Mifeprex to patients going through this process, in order to make it easier and faster. When clinicians are unable to add Mifeprex to their treatment regimen,

many patients and their families suffer both emotional and physical tolls from longer labor inductions.

29. After five years of advocacy and hundreds of hours of advocacy by a few dedicated clinicians and stakeholders, Mifeprex finally became available onsite at the University of Michigan in late September 2019. But even now, the work continues: although Mifeprex is available at the Von Voigtlander Women's Hospital (where the Women's Clinic is located), I am still expending hours of effort to work to make Mifeprex available at our six OB/GYN outpatient sites, where clinicians continue to struggle to develop systems to stock and store Mifeprex consistent with the REMS. As a result, patients in those communities must travel longer distances (up to 40 miles round-trip) to get to our hospital for care, rather than being able to obtain a prescription for Mifeprex at their local outpatient site to then fill through a retail or mail-order pharmacy.

30. The Mifeprex REMS made this process extremely burdensome, requiring both an institutional champion (myself) willing to expend more than 80 hours of work and significant professional capital, and more institutional resources than I have seen for any other medication that has ever been made available in clinic at the University of Michigan. The five-year delay in Mifeprex's availability in clinic harmed patients.

hours of work and significant professional capital, and more institutional resources than I have seen for any other medication that has ever been made available in clinic at the University of Michigan. The five-year delay in Mifeprex's availability in clinic harmed patients.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on April 14, 2021.

Charisse M. Loder, M.D., M.Sc.

EXHIBIT 7

Declaration of Jane Roe, M.D.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAII

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

vs.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]

DECLARATION OF [redacted], M.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

[redacted], M.D., a/k/a/ Jane Roe, M.D., declares and states as follows:

1. I make this declaration based on my own personal knowledge. If called to testify, I could and would do so competently as follows.

2. I am a Family Medicine doctor trained in abortion care. I live and practice in a rural area in the western United States, approximately 100 miles away from the nearest abortion clinic. I am seeking to proceed pseudonymously out of fear of being exposed—nationally and in my small, rural town—as an abortion provider. In light of the extreme harassment and violence, including murder, that has been perpetrated against abortion providers in the United States, I attempt to keep my provision of abortion care as private as possible; I am painfully aware that my primary practice does not have the safeguards in place that exist at the abortion clinics (several hours away) where I work part-time—bulletproof glass, violent intruder protocols, alarm button, separate entrance for providers, and so on. Moreover, given the significant abortion stigma in my community, I expect that I would lose many of my non-abortion patients at my primary practice if the fact of my abortion provision were widely known.

3. I am a member of Plaintiff Society of Family Planning, and I submit this declaration in support of Plaintiffs' Motion for Summary Judgment. I do so only in my individual capacity and not on behalf of any institution with which I am affiliated.

4. Attempting to comply with the Mifeprex REMS has been time-consuming, stressful, and professionally compromising. Because of the REMS, my ability to care for my patients in accordance with their needs and with my medical judgment has been conditioned on my seeking (and gaining) approval and assistance from countless individuals and committees within my health care institution. If not for the REMS, I could have simply written a prescription for Mifeprex for my patients to fill at a local or mail-order pharmacy, rather than having to mount a workplace lobbying campaign, and jeopardize my professional standing, in order to provide this safe medication onsite to my patients who need it.

5. I am a full-spectrum Family Medicine physician. In addition to my three years of residency, I completed a Family Medicine fellowship in obstetrics. I often care for three or four generations within a family—delivering a baby one day and caring for her grandmother the next. I perform a range of obstetric and gynecological services, such as cesarean sections, tubal ligations, leeps (which entails removing pre-cancerous lesions from the cervix), endometrial biopsies, and insertion and removal of intrauterine contraceptive devices.

6. I also provide miscarriage management, including by prescribing medications to evacuate the contents of a patient's uterus. When using medications to manage a miscarriage, it is the standard of care to use both Mifeprex and misoprostol, the same two drugs used in the FDA-approved medication abortion

regimen. Thus, as discussed further below, the restrictions on Mifeprex impact my ability to provide both abortion and miscarriage care.

7. I work at a hospital and affiliated clinic within a large health care system that includes multiple hospitals, each of which has one or more affiliated clinics. Many of my patients are low-income; virtually all are rural; and many travel to us from medically underserved areas in our state. Indeed, some of my patients live in areas where there are no roads—only snowmobile access in the winters.

8. Over the years, my colleagues and I have had multiple patients ask if we could provide a medication abortion, but—because we could not write them a prescription for Mifeprex to fill at a pharmacy—we had to refer all of these patients elsewhere for care. The nearest abortion clinic is a 200-mile round-trip, and some of these patients never made the journey, instead returning later for prenatal care. I recall one adolescent patient who told my colleague that she had repeatedly scheduled appointments at the abortion clinic, only to have to cancel multiple times because she simply could not make it there.

9. So, in February 2017, along with a few colleagues, I began the process of trying to get Mifeprex added to our hospital's formulary. The formulary is the list of medications approved for use by the pharmacy committees for our hospital and for our health care system, and then made available at our hospital for

dispensing or administering to patients. Based on conversations I had with colleagues about attitudes towards abortion at our institution, I concluded that there was a greater likelihood of my gaining approval to add Mifeprex to our formulary and dispense it in my office, rather than gaining approval to perform surgical abortion services in our operating room. That is because the latter would require the involvement of many clinicians, including nursing staff, certified scrub technicians, and anesthesia providers, and would thus require (at a minimum) approval from the CEO of the hospital and the departments overseeing each of those categories of clinicians, as well as the development of opt-out procedures for the supporting clinical staff.

10. Attempting to add Mifeprex to our formulary was a major undertaking. First, we had to obtain approval from the pharmacy committee at our hospital. Once that committee agreed to move forward with the process, we could elevate the request to the pharmacy committee for the entire health care system.

11. Over the next six months, we were delayed time and again in trying to get a decision from that system-level pharmacy committee—including being advised by a representative of the committee to delay raising the issue of Mifeprex until our request could undergo further "informal vetting," and then being bumped from the agenda for the committee's once-a-month meeting at least three times. In addition, the pharmacy committee representative insisted that *we* complete the

"new drug review" analysis for Mifeprex—a time-consuming assignment that, to my knowledge, is always completed by the system-level pharmacy committee, not by the hospital-level pharmacy committee or the individual physicians or pharmacists making the request. I believe this was demanded of us only because of the controversy and stigma surrounding abortion in our community, as in many places in this country.

12. Throughout the six months that we were slogging through this process—which would not have been necessary if not for the REMS—I was forced to turn away patients who needed my care. I know with certainty that, as a result, at least one of my patients was delayed past the point in pregnancy when she could obtain a medication abortion at all—which is available only up to 10 weeks of pregnancy—and had to travel 200 miles round-trip to have a surgical abortion instead. While abortion is one of the safest procedures in modern American medicine, and far safer for a woman than remaining pregnant and carrying to term, the risks associated with abortion increase as pregnancy advances. Thus, delaying a woman's abortion care increases the risks she faces.

13. It is inconsistent with both my medical judgment and my deeply held values to deny a patient's urgent request for time-sensitive medical care that I am qualified to provide—but that is exactly what the REMS required of me.

14. In September 2017, I was contacted by the Chief Medical Officer of

our health care system, who had apparently been informed of my request. To my knowledge, it is very unusual for the CMO to be involved in a formulary request, and I assume that my request was only elevated to this very high level because of the controversy surrounding abortion. He proposed a possible strategy to enable me to provide Mifeprex to my patients while avoiding the conflict that he expected would result from a system-wide debate on this question: namely, that I would prescribe and dispense Mifeprex as a "non-formulary drug," which the policy defines as "[a]n agent, which has not been reviewed by the [pharmacy committee] or has been reviewed and denied admission to the formulary."

15. This was a highly unusual application of our policy on non-formulary drugs, which to my knowledge is typically invoked in situations where patients admitted to our hospital need to continue a pre-established medication regimen for the short period of time that they are admitted. The policy on non-formulary drugs also expressly provides that usage of such medications will be "tracked and routinely reviewed . . . to evaluate appropriateness" by the system-level pharmacy committee—the very same committee that this strategy was designed to avoid, given the expectation of conflict over the abortion issue. Classifying Mifeprex as a non-formulary drug to be "tracked and routinely reviewed" meant that I had to continue to expend time, and put my professional reputation on the line, having discussions with leadership at my institution regarding my Mifeprex use. And, of

course, this designation meant that I could suddenly lose the ability to provide this care to my patients.

16. After gaining this temporary, precarious approval to stock and dispense Mifeprex on-site as a non-formulary drug, I next had to sign up with Danco (the manufacturer of Mifeprex) as a certified prescriber and set up an account with the drug distribution company. This was a significant ordeal in and of itself, further delaying my ability to care for my patients by approximately two months. I completed as much of the paperwork myself as I could, but setting up an account requires information (including on billing and shipping) that, as a doctor within a large health care institution, I do not have. This meant that I had to involve yet another colleague in the process—my Practice Administrator, who oversees finances, staffing, and other significant matters in our practice—and then repeatedly bother that person, who I know to be personally opposed to abortion, until it got done. If not for the REMS, I would not have had to compromise this important professional relationship in this manner.

17. I believe that the REMS has harmed my reputation among some of my colleagues by necessitating that I engage in an internal lobbying campaign to try to make Mifeprex available onsite, and necessitating the involvement of additional members of our staff in this care. For instance, I was informed about a senior leadership meeting at which a colleague raised as a "concern" that I was working

to make Mifeprex available at our facility (mentioning me by name).

18. *None* of this would have been necessary if I could simply write a prescription for Mifeprex for my patient to fill at a retail pharmacy, as I can do for virtually every other prescription drug. My colleagues do not have to expend such time and resources, or jeopardize their professional reputations, in order to prescribe other medications that are equally or less safe than Mifeprex.

19. Earlier in 2019, our health care system finally approved Mifeprex as a formulary drug. But this was no quick fix: ordering, stocking, and dispensing the medication remains a complicated, multi-stage process involving numerous staff members across our health care system. To begin, one provider from each individual clinic or hospital wishing to prescribe Mifeprex must register with the "buyer" for our health care system's central pharmacy. This entails attesting that they will oversee the prescription and dispensing of Mifeprex at their clinic or hospital site; completing the necessary materials for Danco; determining how many doses to order; and all of the correspondence and paperwork this necessitates. The central pharmacy then orders the medication to be stocked at the specific clinic or hospital.

20. In the Family Medicine clinic where I work, Mifeprex is stored under lock in our medication stock room, where we keep vaccines and other medications administered in the clinic (typically drugs administered by injection, or basic

painkillers like ibuprofen). When one of the medical assistants who works in my clinic sees that I have entered an order for Mifeprex, she goes into the medication stock room to obtain the pill and complete the special Mifeprex log, noting the serial number of the package (as required by the REMS) as well as the two-part patient ID (typically, the patient's medical records number and date of birth).

21. Having to comply with the REMS thus dramatically increases the number of people in our health care system who must be involved in the provision of Mifeprex. In addition to posing logistical complications, this heightens the risk of a violation of patient confidentiality—and perpetually threatens that a single individual who opposes abortion could delay or derail the process. By contrast, if not for the REMS, I could just electronically submit the prescription order to a pharmacy of my patient's choice and no one else would have to be involved.

22. Notably, formulary drugs are still subject to "annual" review by the system-level pharmacy committee (as compared to the "routine" review for non-formulary drugs)—which means that availability at our hospital is still subject to debate every year by a committee, the members of which change on a regular basis. My ability to include Mifeprex within my practice, and my patients' access to this vital care, remains precarious.

23. The Mifeprex REMS also requires me to provide my patients with and discuss, and for us each to sign, a "Patient Agreement Form" containing medical

information about Mifeprex dated to March 2016. This is not merely unnecessary from an informed consent perspective—it actively *undermines* my informed consent process by forcing me to discuss with my patients information that is inconsistent with my clinical approach and increasingly out-of-step with the research on Mifeprex as science moves forward. For instance, the form requires the patient's signature that, "[i]f my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy." However, I (like many clinicians) treat the small percentage of patients whose pregnancies continue following use of the Mifeprex and misoprostol regimen with additional medication doses in the first instance, not surgery. This is well within the standard of care, yet not reflected in the form—to the contrary, the form suggests to patients that surgery is the *only* option in such a case. Moreover, the statement that "the treatment will not work . . . . in about 2 to 7 out of 100 women" is misleading and not how I counsel my patients about the expected efficacy of the treatment: while in some small number of cases, the regimen listed on the label will not fully complete the abortion, the treatment may very well still work – after, for instance, an additional dosage of misoprostol.

24. The Form is particularly ill-suited for my patients to whom I am prescribing Mifeprex as part of miscarriage management, as has become the standard of care. The Form does not describe the clinical circumstances of patients

experiencing pregnancy loss, and can be confusing and distressing for them. Nevertheless, because of the REMS, I still must have these patients sign the Form before I can prescribe them Mifeprex. For all of these reasons, the Patient Agreement Form interferes with my ability to practice my profession in accordance with my medical judgment.

25. I hope that more clinicians within our health care system will begin providing Mifeprex at their own hospitals and clinics as well, and thus continue to expand access to this safe and effective medication. I have had numerous conversations with like-minded colleagues to that end, including giving them advice about navigating the multi-step, time-consuming process I described above to register with both our health care system and with Danco as a prescriber and then to actually get the medication onsite. Unfortunately, these logistical hurdles caused by the REMS have proven to be a significant deterrent, and there are still only a handful of us in the health care system who prescribe Mifeprex, either for abortion care or for miscarriage management.

I declare under penalty of perjury that the foregoing is true and correct.

Executed in [redacted], on [redacted], 2021.

[redacted]

[redacted], M.D., a/k/a Jane Roe, M.D.

EXHIBIT 8

Declaration of Diana M. Pearce, Ph.D.
& Pearce Decl. Appendix

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

vs.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]

DECLARATION OF DIANA M. PEARCE, PH.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

Diana M. Pearce, Ph.D., declares and states as follows:

I. BACKGROUND AND QUALIFICATIONS

1. I make this declaration based on my own personal knowledge. If called to testify, I could and would do so competently as follows.

2. I provide the following facts and opinions as an expert in the field of Sociology, specifically specializing in poverty, women's welfare, and women studies in the United States. I hold an M.S.W. and a joint Ph.D. in Social Work and Social Science (Sociology) from the University of Michigan. I am currently the Scholar in Residence at the Center for Women's Welfare at the School of Social Work at the University of Washington, after serving as the Founder and Director of the Center for 18 years. For more than two decades, I have been on the faculty of the School of Social Work as a Senior Lecturer (now Senior Lecturer Emerita), as well as an affiliate of the Gender, Women and Sexuality Studies department and the West Coast Poverty Center, all at the University of Washington. For over 40 years, I have conducted research and published on the topics of poverty and women's welfare in peer-reviewed sociology and poverty journals. Most famously, I coined the term "the feminization of poverty,"[1] which became one of the ten themes of the Beijing Conference on Women in 1995, as well as the subject of countless articles and books.

[1] Diana M. Pearce, *The Feminization of Poverty: Women, Work and Welfare*, 11 Urb. & Soc. Change Rev. 28 (1978).

I have also authored numerous reports, including for the U.S. Department of Labor and the U.S. Civil Rights Commission.

3. Since 1996, I have been the creator and principal investigator of the Self-Sufficiency Standard (the "Standard"), which measures the amount of income necessary for different family types to meet basic needs without public subsidies or private/informal assistance. Since then the Standard has been calculated for 41 states.[2]

4. I have presented my research on poverty at numerous professional conferences and governmental briefings, including presentations to the U.S. Department of Health and Human Services and the U.S. House of Representatives. I also testified twelve times before the U.S. Congress. I have received various awards for my work and research, including:

- National Association of Social Workers, Presidential Award for Leadership in Research (presented at NASW Conference, The Feminization of Poverty Revisited) (2013)
- Wider Opportunities for Women, Setting the Standard (Lifetime Achievement) Award (2003)
- Workforce Development Council of Seattle-King County, for Visionary Research on Family Self-Sufficiency (2003)
- Society for Applied Sociology, Sociological Practice Award (2003)

[2] For all data and reports relating to and a general explanation of the Standard, see generally Self-Sufficiency Standard, http://www.selfsufficiencystandard.org/ (last visited Apr. 7, 2021).

5. A true and correct copy of my curriculum vitae is attached as Exhibit H-1 to this declaration.

II. THE IMPACT OF THE RISK EVALUATION AND MITIGATION STRATEGY (REMS) FOR MIFEPREX ON WOMEN SEEKING ABORTION CARE

6. I have been asked to evaluate the impact of the Mifeprex REMS on women in the United States seeking abortion care.[3] I understand that under the Mifeprex REMS, a patient cannot obtain the medication by prescription at a retail pharmacy or by mail; they must receive it at a clinic, medical office, or hospital from a clinician who has prearranged to stock and dispense Mifeprex. I understand that these requirements deter or prevent a significant number of health care providers, such as Dr. Graham Chelius on Kaua‘i, from prescribing medication abortion, and, as a result, some patients have to travel further distances or make an entirely unnecessary trip in order to access time-sensitive abortion care. I understand further that the REMS prevents medication abortion patients who have been evaluated and counseled via telemedicine from picking up their prescription at their local pharmacy or obtaining their mifepristone prescription by mail without even having to leave home, forcing such patients instead to make a trip to a REMS-certified provider just to pick up the pill and sign a form.

[3] I use “women” here as a shorthand for patients who need abortion care, but note that patients who are gender non-binary or transgender also utilize these services.

7. Data demonstrate that the overwhelming majority of abortion patients are low-income and struggle to make ends meet. As an expert in poverty and women's welfare who has studied the barriers that affect low-income women's access to health care, I know that low-income people find it extremely difficult just to afford their basic household needs, let alone unplanned emergency expenses like abortion. In my expert opinion, by requiring patients to make additional and/or lengthier trips to get a medication abortion, the Mifeprex REMS increases the costs and logistical burdens of accessing care—including missed work, transportation and child care costs—to such a degree that they significantly delay or entirely prevent women from accessing abortion care. Even for those who are ultimately able to access care, the resources and other hurdles that the REMS force women to navigate often require significant sacrifices for patients and their families that threaten patients' privacy and economic stability, including by jeopardizing their employment or housing, forcing patients to forgo other necessary expenses like food or other medical care, and increasing the risk of domestic violence.

A. Many Abortion Patients Cannot Afford to Meet Their Basic Needs.

8. The vast majority of women seeking abortion care have low incomes. In 2014, the most recent year for which data are available, half (49%) of women seeking abortions in the United States had incomes at or below the U.S. Official Poverty Measure (OPM), which for 2014 was $11,670 annually for a single person

or $19,790 for a family of three (in the contiguous U.S.).[4] Another quarter (26%) of U.S. abortion patients had incomes between 100 and 200% of the OPM in 2014.[5] In other words, based on the OPM, three out of four abortion patients are poor or very low-income.[6]

9. But it is likely that this statistic actually undercounts the percentage of abortion patients with inadequate income to meet their basic needs, because the OPM is based on a flawed and outdated methodology and set of assumptions. The OPM was developed decades ago and assumes that a family's total budget is three times what they spend on food—reflecting average American family expenditure patterns of the mid-1950s. However, household expenditure patterns have changed significantly since then. For instance, the cost of food has increased much less over

[4] Jenna Jerman, Rachel K. Jones & Tsuyoshi Onda, Guttmacher Inst., Characteristics of U.S. Abortion Patients in 2014 and Changes Since 2008 1, 7 (2016), https://www.guttmacher.org/report/characteristics-us-abortion-patients-2014; *Prior HHS Poverty Guidelines and Federal Register References*, U.S. Dep't of Health & Hum. Servs., https://aspe.hhs.gov/prior-hhs-poverty-guidelines-and-federal-register-references (last visited April 7, 2021). For 2021, the amounts are $12,880 for a single person and $21,960 for a family of three. *2021 Poverty Guidelines*, U.S. Dep't of Health & Hum. Servs.: ASPE (last updated Jan. 26, 2021), https://aspe.hhs.gov/2021-poverty-guidelines.

[5] Jerman, Jones & Onda, *supra* note 4, at 1, 7.

[6] *Id.* Because these statistics are drawn from surveys of patients who received an abortion, they do not account for poor or low-income patients who wanted to have an abortion but were prevented from accessing one because of financial or other barriers to access. *Cf., e.g.*, Sarah C.M. Roberts et al., *Out-of-Pocket Costs and Insurance Coverage for Abortion in the United States*, 24 Women's Health Issues e211, e215 (2014), https://www.sciencedirect.com/science/article/abs/pii/S1049386714000048 (in longitudinal study of abortion patients at 30 facilities across the country, more than half reported that the need to raise money delayed access to care).

the past decades than almost all other basic expenses, while other costs have increased substantially (housing, health care, taxes). Moreover, the OPM does not account for geographic variation in costs or for variations in family type (such as by children's ages), and it does not explicitly reflect basic needs like child care, taxes, health care, and transportation.[7]

10. A more accurate measure of income inadequacy is the Self-Sufficiency Standard, which my colleagues and I first developed two decades ago to address gaps and deficiencies in the federal poverty measures. The Self-Sufficiency Standard describes the minimally adequate income that a family of a certain composition in a given place needs to meet their basic needs, without public or private assistance. It is tailored to reflect the minimum actual costs of housing, child care, food, transportation, health care, miscellaneous expenses, taxes, and tax credits for 719 family types in every county in a given state. The Standard additionally reflects cost

[7] Increasing recognition of the OPM's shortcomings led Congress in the 1990s to direct the National Academies of Sciences, Engineering and Medicine to undertake a wide-ranging study of the measure. *See* Nat'l Rsch. Council, Measuring Poverty: A New Approach xv, 2–3 (Constance F. Citro & Robert T. Michael, eds. 1995), https://www.nap.edu/download/4759#. The study and resulting report spurred a number of experimental measures piloted by the U.S. Census Bureau, and, in 2010, the Bureau adopted the Supplemental Poverty Measure (SPM). *See* Liana Fox, U.S. Census Bureau, The Supplemental Poverty Measure: 2019 (2020), https://www.census.gov/library/publications/2020/demo/p60-272.html. Although the SPM addresses some of the problems with the OPM, such as varying housing costs by Census region, it does not consider the substantial variation in housing costs within the four Census regions, and it either fails to or inadequately addresses the other flaws discussed above. In particular, the SPM methodology does not address the most serious shortcoming of the OPM— that it seriously underestimates the total cost of basic needs—and thus like the OPM, the SPM is likewise much too low, everywhere and for every family type.

differentials due to the age of children; thus, families with children below school age requiring full-time child care will have a higher Standard than those with older or no children. Whenever possible, the amount for a given need is based on the amount of financial assistance that the government (federal or state) has deemed minimally adequate for that basic need (such as housing, child care, or food expenses).[8]

11. We have found that a substantial percentage of people across the country—and far more than are captured by the OPM—do not have incomes sufficient to meet their basic needs.[9] (This is true even though the vast majority of households with incomes below the Standard have at least one worker in them.[10]) The Standard is higher than the OPM in every jurisdiction for which we have

[8] For housing, the Standard uses the U.S. Department of Housing and Urban Development Fair Market Rents, which set the maximum rent allowed for Section 8 voucher (housing assistance) recipients; for child care costs, the Standard uses the maximum amount set by the state for reimbursement for those receiving child care assistance (minus child care copayments); and for food costs, the Standard uses the U.S. Department of Agriculture's "Low-Cost" Food Plan, which only covers the cost of basic groceries, with no allowance for any take-out or restaurant food. L. Manzer & A. Kucklick, Ctr. for Women's Welfare, Technical Brief: The Self-Sufficiency Standard 2021 Update (2021) (available upon request from the Center for Women's Welfare, University of Washington School of Social Work, www.selfsufficiencystandard.org).

[9] When calculating income inadequacy compared to the Standard, we consider all cash resources available to a household, including cash assistance, such as Temporary Assistance for Needy Families (TANF) or Supplemental Security Income (SSI). It should be noted, however, that the income limits for means-tested cash assistance are very low (often near or even below the OPM), and thus are never sufficient to bring a family up to their Self-Sufficiency Standard.

[10] *See, e.g.*, Diana M. Pearce, Ctr. for Women's Welfare, Overlooked and Undercounted 2018: Struggling to Make Ends Meet in Colorado, at vi (2018), http://www.selfsufficiencystandard.org/sites/default/files/selfsuff/docs/CO18_Demo_Web.pdf.

calculated it—sometimes significantly higher.[11] This is especially true for families—which is notable here since, nationwide, about 60% of women seeking an abortion have at least one child.[12]

12. In fact, the Self-Sufficiency Standard for a family consisting of one adult and one infant exceeds *200% of the OPM* in 92% of counties in the 31 states for which we have current Standard data and in every single county in 20 states. And the gaps are similarly stark for other family types.[13] In other words, given that the Standard is a bare-bones budget, it is clear that in the vast majority of counties in most states, abortion patients with incomes living up to 200% of OPM still lack the minimum income necessary to afford even their basic household needs.

13. My research in numerous states to determine the characteristics of households most likely to have income below the Self-Sufficiency Standard further reinforces the existing data showing that most abortion patients struggle to make ends meet. As noted, a majority of abortion patients are mothers,[14] and

[11] The states with current Standard data included in this analysis are: AL, AZ, CA, CO, CT, FL, GA, HI, IL, IN, KS, MA, MD, MI, MN, MO, NC, NJ, NV, NY, OK, OR, PA, SC, TN, TX, UT, VA, WA, WI, and WY. Data on file with the author.

[12] *Abortion Surveillance — United States, 2018*, Ctrs. for Disease Control & Prevention, at Table 7 [hereinafter "*CDC Abortion Surveillance*"], https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7_down (last updated Nov. 7, 2020).

[13] For a family of one adult and one preschooler, the Standard exceeds 200% of the OPM in 88% of counties; for a family with one adult, one preschooler, and one school-aged child, in 83% of counties; and, for a family with two adults, one preschooler, and one school-aged child, in 84% of counties.

[14] *CDC Abortion Surveillance*, *supra* note 12, Table 7.

approximately 85% are unmarried.[15] Moreover, 60% identify as people of color, including 53% identifying as Black or Hispanic.[16] My colleagues and I have uniformly found that these are the very populations that are statistically more likely than other demographic groups to live below the Standard.

14. For example, the percentage of Black households with incomes below the Standard is on average double the percentage of white households with incomes below the Standard; the percentage of Latinx households is 2.5 times the percentage of white households; and the percentage of single-mother families with incomes below the Standard is 2.2 times that of married couples with children.[17] This is particularly true for single mothers of color: on average, almost three out of four (74%) Black single mothers, and almost four out of five (79%) Latina single mothers, have incomes below the Standard.[18]

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[15] *Id.* at Table 6, https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T6_down.

[16] *Id.* at Table 5, https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down; *see also* Jerman, Jones & Onda, *supra* note 4, at 1, 5.

[17] Based on an analysis of Standard data and demographic reports for California (2019), Colorado (2016), Connecticut (2017), Maryland (2015), New York City (2019), New York State (2019), Pennsylvania (2017), Washington (2013), and Wyoming (2010–2014). Data on file with the author and/or available on the Standard website, in individual reports. *See Self-Sufficiency Standard by State*, Self Sufficiency Standard, http://www.selfsufficiencystandard.org/self-sufficiency-standard-state (last visited Apr. 8, 2021); *Research and Resources: Demographic Reports*, Self Sufficiency Standard, http://www.selfsufficiencystandard.org/node/30 (last visited Apr. 8, 2021).

[18] In every state for which we have performed these demographic analyses, at least 65% of Black single mothers and 74% of Latina single mothers had incomes below the Standard, compared to an average of 52% of white single mothers. See resources listed above, *supra* note 17.

15. To further illustrate this concept, consider Kaua'i. On that island, where Dr. Chelius's patients live, the 2020 Self-Sufficiency Standard—the *minimum* income necessary for basic subsistence, based largely on government reimbursement rates—for a single adult caring for one school-aged child and one preschooler was nearly 1.75 times the median household income for single-mother households in Kaua'i, and more than triple the 2020 OPM for a family of three.[19] For a single adult caring for one infant, the Standard was 1.8 times higher than the median income for single mothers in Kaua'i, and more than four times the 2020 OPM for a family of two.[20] Thus, many single-mother households in Kaua'i that would not be classified as poor or low-income according to the OPM are in fact struggling to afford basic household needs.

16. Kaua'i is not an outlier. I analyzed the monthly basic needs budget for families with one adult and one preschooler in the least expensive county, median county, and county with the largest city in eight representative states across the

[19] *Compare Hawaii Self-Sufficiency Standard Table, 2020*, at By County tab, Table 3, cell L71 (2020) [hereinafter "*Hawaii Standard 2020*"], http://www.selfsufficiencystandard.org/node/50 (Self-Sufficiency Standard of $69,224), *with* U.S. Census Bureau, *Table S1903: Median Income in the Last 12 Months*, https://data.census.gov/cedsci/table?q=S1903&tid=ACSST1Y2019.S1903 (filter by "Browse Filters: Geography," "Geography: County," "Within (State): Hawaii," and select "Kauai County, Hawaii) (last visited April 7, 2021) (median income of $39,422 for "Female householder, no spouse present" and "With own children under 18 years"), *and 2020 Poverty Guidelines*, U.S. Dep't of Health & Hum. Servs.: ASPE (last updated Jan. 21, 2020), https://aspe.hhs.gov/2020-poverty-guidelines (2020 OPM of $21,720).

[20] *Compare Hawaii Standard 2020*, *supra* note 19, at By County tab, Table 3, cell C71 (Self-Sufficiency Standard of $70,788), *with* U.S. Census Bureau, *Table S1903*, *supra* note 19 (median income of $39,422), *and 2020 Poverty Guidelines*, *supra* note 19 (2020 OPM of $17,240).

country, all of which have statewide poverty rates (according to the OPM) similar to either the national average or the average for their geographic region.[21] In every county in every state considered in this analysis, a full-time minimum wage worker[22] is unable to afford the minimum needs for their family. In all eight states, one adult with a preschool-aged child in the least expensive county in the state (*i.e.*, the county with the *lowest* Standard) needs at least 36% more than a full-time minimum wage income (Santa Cruz County, AZ) and as much as two or more times the minimum wage (Uvalde County, TX, and Person County, NC), just to afford their family's basic needs. For those living in the largest city in each of these states, the deficit is even more substantial: in Chicago (Cook County, IL), a single mother with a preschooler needs to earn almost twice the minimum wage, while in Charlotte, NC (Mecklenburg County), she needs to earn at least 3.6 times the minimum wage, just to meet her basic needs. These families are already forced to make sacrifices or economic trade-offs just to scrape by; *any* added expense, no matter how small, can be destabilizing, potentially forcing them to forgo basic needs like food, rent, or

[21] States used in this analysis are those (a) with statewide poverty rates closest to the national rate or to the average rate for states in their Census region, based on data from the U.S. Census Bureau, and (b) for which current Self-Sufficiency Standard data (2021) was available. *See* Exhibit H-2 (summarizing Standard data for all 8 states).

[22] The Standard assumes full-time work (40 hours per week). Thus, I am evaluating whether full-time work at the state (or local) minimum wage will be enough to meet the cost of basic needs in the Standard for this family type in each place.

medical care.[23]

17. Key economic trends indicate that American families may be facing even more challenges in the future. For example, in every state in which my colleagues and I have tracked the Standard over the last two decades, the cost of basic needs has been rising faster than income, even during the Great Recession and the subsequent Recovery.[24] In addition, the economic precarity of many working families across the country has only been amplified by the current economic recession relating to the COVID pandemic. While the data showing the full extent of the economic impact of the pandemic is not yet available, and uncertainty remains due to new surges in COVID cases, the widespread job losses and staggeringly high rates of unemployment experienced so far already have taken their toll, with large

[23] For many families, public assistance will be inadequate to fill these gaps. For example, as its name suggests, the Temporary Assistance for Needy Families Program (TANF) is not designed to be an ongoing source of income for working families; although work is required to maintain eligibility, even working part-time is likely to result in an income too high to maintain eligibility for TANF. And while in-kind benefits such as SNAP (food stamps), child care assistance, and housing assistance are meant to help low-wage workers, only a minority of eligible families actually receive those benefits. *See, e.g.*, Gov't Accountability Office, Child Care: Subsidy Eligibility and Receipt, and Wait Lists – Briefing to Senate Comm. on Health, Educ., Labor & Pensions and House Comm. on Educ. & Labor, GAO-21-245R, at 12 (2020), https://www.gao.gov/assets/gao-21-245r.pdf (only 14% of children eligible for child care assistance under federal standards, and only 22% of those eligible under state rules, actually receive such assistance in an average month); G.T. Kingsley, Urban Institute, Trends in Housing Problems and Federal Housing Assistance3 (2017), https://www.urban.org/sites/default/files/publication/94146/trends-in-housing-problems-and-federal-housing-assistance.pdf (only about one in five low-income renters with housing needs received assistance in 2015).

[24] For example, see Standard Reports for Colorado, Connecticut, Indiana, Maryland, Michigan, New York, New York City, North Carolina, Ohio, Oregon, South Carolina, Washington, Wisconsin, and Wyoming, all available at *Self-Sufficiency Standard by State*, *supra* note 17.

numbers of families citing serious economic impacts and concerns for the future.[25] These losses have disproportionately affected single mothers, particularly women of color, and other households that had inadequate income to meet their basic needs even before the recession.[26]

18. In sum, in considering the impact of the Mifeprex REMS on access to abortion nationwide, it is important to recognize that the vast majority of abortion patients—likely even *more* than the 75% of patients with incomes at or below 200% OPM—are already unable to afford their and their families' basic needs. For these patients, the unexpected, emergency expenses associated with traveling for abortion care—whether to another county, city, or state, or even to a second local health care facility—presents a serious hardship or is entirely impossible.

B. The Mifeprex REMS Imposes Significant Costs and Burdens on Medication Abortion Patients.

19. Abortion access is very limited in the United States. Approximately 90

[25] J. Horowitz et al., *A Year Into the Pandemic, Long-Term Financial Impact Weighs Heavily on Many Americans*, Pew Rsch. (Mar. 5, 2021), https://www.pewresearch.org/social-trends/2021/03/05/a-year-into-the-pandemic-long-term-financial-impact-weighs-heavily-on-many-americans/ (finding that 40% of adults say they or someone in their household lost a job or wages during the pandemic, and half of those who did so are still earning less than before the pandemic).

[26] *See id.* (finding that, during the pandemic, Black and low-income workers are more likely to have incurred debt or put off paying household bills due to lost income); A. Barroso & R. Kochhar, *In the pandemic, the share of unpartnered moms at work fell more sharply than among other parents*, Pew Rsch. (Nov. 4, 2020), https://www.pewresearch.org/fact-tank/2020/11/24/in-the-pandemic-the-share-of-unpartnered-moms-at-work-fell-more-sharply-than-among-other-parents/ (finding steepest declines among Black and Hispanic single mothers and single mothers with young children).

percent of U.S. counties lack an abortion clinic, and, nationwide, 38% of women of reproductive age live in those counties.[27] A survey of a nationally representative sample of more than 8,000 abortion patients found that the average distance traveled to reach the clinic was 68 miles round-trip.[28] In a majority of states, at least one in five women of reproductive age lives more than 50 miles from the nearest clinic.[29] While rural women are most likely to face significant travel distances,[30] women in many cities must also travel significant distances to obtain abortion care: for instance, a 2018 study characterized 27 major U.S. cities as "abortion deserts" because they did not have a publicly advertised facility that provides abortions within 100 miles.[31]

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[27] Rachel K. Jones & Jenna Jerman, *Abortion Incidence and Service Availability in the United States*, *2014*, 49 Persp. on Sexual & Reprod. Health 17, 20 (2017), https://onlinelibrary.wiley.com/doi/epdf/10.1363/psrh.12015. Today, 95% of abortions are performed in clinics (rather than doctors' offices or hospitals). *Id.* at 17.

[28] Liza Fuentes & Jenna Jerman, *Distance Traveled to Obtain Clinical Abortion Care in the United States and Reasons for Clinic Choice*, 28 J. Women's Health 1623, 1625 (2019), https://pubmed.ncbi.nlm.nih.gov/31282804/.

[29] Jonathan M. Bearak et al., *Disparities and Change Over Time in Distance Women Would Need to Travel to Have an Abortion in the USA: A Spatial Analysis*, Lancet Pub. Health e493, e495–96 (2017), https://www.thelancet.come/action/showPDF?pii=S2468-2667%2817%2930158-5 (in six states, a majority live more than 50 miles away, including two where a majority live more than 150 miles from the nearest provider).

[30] *See, e.g.*, Nicole E. Johns et al., *Distance Traveled for Medicaid-Covered Abortion Care in California*, 17 BMC Health Serv. Res. 287, 294 (2017), https://doi.org/10.1186/s12913-017-2241-0 (more than half of rural women in California traveled more than 50 miles to obtain an abortion); Bearak et al., *supra* note 29, at e497 (identifying swath of rural counties in the middle of the United States with travel distances of more than 180 miles to nearest abortion clinic).

[31] Alice Cartwright et al., *Identifying National Availability of Abortion Care and Distance from Major US Cities: Systematic Online Search*, 20 J. Med. Internet Res. 7 (2018), https://www.jmir.org/2018/5/e186/.

20. I understand that the Mifeprex REMS increases the distance that many women must travel to obtain a medication abortion, both by diminishing the number of medication abortion providers across the country (thus increasing the distance or number of trips patients must make to access care), and by preventing medication abortion providers from delivering mifepristone care to their eligible patients using telemedicine and mail (*i.e.*, but for the REMS, those patients would not have to travel at all to get the care they need).

21. As detailed below, the costs and burdens associated with increased travel and/or multiple trips to obtain an abortion typically include transportation, child care, and missed work, and may also include lodging, increased food costs (while traveling), and other unexpected expenses. There are also nonfinancial costs, as the logistics and time associated with travel, and the need to raise money for travel and associated costs, will often require the patient to share the fact of her abortion with people, such as household members and employers, whom she otherwise would not wish to tell—which may put her at risk for domestic violence or jeopardize her employment.

22. In my expert opinion, the overwhelming majority of people seeking abortions nationwide who have incomes too low to meet their basic needs—at *minimum*, three out of four abortion patients—suffer significant harm as a result of these added costs and burdens. Many are delayed in accessing this time-sensitive

care while they raise funds and make travel and logistical arrangements; some are blocked from obtaining an abortion at all because they cannot afford and navigate these costs and complications, or because they cannot safely share their abortion decision with household members or employers. Even those who are able to obtain an abortion despite these hurdles will have to make harmful trade-offs to do so—such as forgoing groceries or other medical care for themselves or their families, failing to pay bills including those for heat or rent, which puts the family at risk of losing their utilities or housing, or otherwise incurring debts that could have long-term consequences for household stability—or be forced to compromise their privacy and safety to access care.

Travel and Transportation

23. The additional travel costs necessitated by the REMS in order to access a medication abortion impose substantial burdens for low-income women. Even local trips of relatively short distances can present significant financial and logistical challenges for low-income women, who—as discussed above—are typically already struggling to afford basic household needs. And those costs and burdens are compounded for patients who live a considerable distance from the nearest medication abortion provider and who may have to incur significant financial costs for transportation, time off from work, child care, and potentially meals away from home, and lodging in order to access care.

24. For people with incomes below the minimum basic needs budget for their area, *any* added expenses—like refilling a gas tank, or taking a relatively short taxi ride—can stretch already strained and overextended budgets. The logistical burdens of arranging a trip to a REMS-certified provider can be especially challenging for those living in the majority of places in the United States with limited or essentially no public transportation options, particularly given that 9% of all households in the U.S. and 24% of households with incomes below the OPM do not have a vehicle, or have access to a vehicle.[32] Even if a low-income woman has access to a car, it may be shared among multiple people, which can limit access in practice, thus delaying care or forcing patients to disclose their abortion to others.

25. These burdens are compounded for those women who live farther from a REMS-certified provider and who may have to travel outside their county or state to access care. Cars owned by low-income households are older on average[33] and therefore less dependable for long journeys. And, for those without access to a

[32] *See* N. McGuckin & A. Fucci, U.S. Dept. of Transp., Summary of Travel Trends 2017 National Household Travel Survey 60, at Table 17, (2018) [hereinafter "NHTS 2017 Summary"], https://nhts.ornl.gov/assets/2017_nhts_summary_travel_trends.pdf; U.S. Dep't of Transp., Fed. Highway Admin., FHWA NHTS BRIEF 2014: Mobility Challenges for Households in Poverty 2. (2014), https://nhts.ornl.gov/briefs/PovertyBrief.pdf.

[33] NHTS 2017 Summary, *supra* note 32, at 8, 20; *see also* Jenna Jerman et al., *Barriers to Abortion Care and Their Consequences For Patients Traveling for Services: Qualitative Findings from Two States*, 49 Perspectives on Sexual & Reprod. Health 95, 98 (2017) (in qualitative study of abortion patients in New Mexico and Michigan who crossed state lines or traveled long distances, factors including "limited access to safe and reliable transportation, or the need to use multiple means of transport[] significantly increased the time it took women to travel even relatively short distances" to access abortion care).

private car, bus or other transportation options between cities may be limited or inaccessible. For example, for a patient in Phillipston, MA,[34] there are abortion providers approximately 30 miles away in Worcester, MA,[35] and Keene, NH. But given limited public transportation options, traveling to Worcester would take at minimum 4 hours and three bus transfers, at an estimated round-trip cost of $42.50[36]; traveling to Keene, NH, would require five transfers and more than a day of travel.[37] For a patient in Cullowhee (Jackson County), NC, there are no public transportation options available to the nearest provider approximately 50 miles away in Asheville;

[34] With the exception of Kaua‘i, Hawai‘i, all other locations used to provide examples of travel distances, routes, and costs in this section are drawn from the same subset of counties in states with poverty rates similar to regional and national averages listed in Exhibit H-2.

[35] All distances to nearest providers are based on a search of publicly listed abortion clinics via Planned Parenthood, https://www.plannedparenthood.org/ (last visited Apr. 8, 2021), and *Find a Provider*, National Abortion Fed’n, https://prochoice.org/patients/find-a-provider/ (last visited Apr. 8, 2021). Driving distances in this section are estimated using Google Maps, assuming uncongested travel times. Bus, train, and flight fares assumed travel within two weeks of search.

[36] *See MART Trip Planner*, Montachusetts Reg’l Trans. Auth., http://www.mrta.us/trip-planner (search start: “Phillipston, MA,” and finish: “Worcester, MA”). The Athol Link bus service departs Phillipston approximately every 90 minutes between 5:45 a.m. and 6:00 p.m., Monday through Friday. Patients would need to transfer at the Gardner City Hall stop to the Wachusett Shuttle line, which, at the time of search, was operating on a limited schedule of only four departures per day (6:05 a.m., 8:20 a.m., 1:05 p.m., and 6:05 p.m.). Patients would then need to transfer again at the MART Intermodal Transportation Center to the Clinton-Worcester Commuter Shuttle (commuter line, only running in morning hours) or the Worcester Shuttle (only three departures per day) for service to downtown Worcester. For full route schedules and fares, see *Routes and Schedules*, Montachusetts Reg’l Trans. Auth., http://www.mrta.us/routes-schedules (last visited Apr. 9, 2021), and *Fares and Passes*, Montachusetts Reg’l Trans. Auth, http://www.mrta.us/farespasses (last visited Apr. 9, 2021). Patients would also need to arrange transportation from home to the departure station and from the arrival station to the clinic.

[37] *See MART Trip Planner*, *supra* note 36. Although my search identified other clinics within 50 miles of Phillipston, travel by public transportation was similarly complicated for all options, involving multiple transfers and multiple-hour trips.

she would have to take a taxi all the way to the outskirts of the city to reach the closest bus stop, at a cost of $140–170.[38] For the families living below the Self-Sufficiency Standards for those states, these added expenses and lengthy travel time—not to mention the time and effort necessary to navigate multiple bus schedules and transfers in potentially unfamiliar locations—may be insurmountable.

26. Furthermore, routes and departure times are often very limited—even more so now, as some services reduced routes during the pandemic and have not yet resumed full service. If available arrival times do not align with available appointment times, even trips of only moderate distance may turn into more expensive cab rides,[39] or require overnight stays, requiring lodging and increasing child care costs and time away from work.

27. The burdens continue to increase for the sizeable percentage of women traveling especially long distances of 100 miles or more each way to access abortion care,[40] such as those in Quartzsite, AZ (La Paz County), who must travel

[38] *See* Rome2Rio, https://www.rome2rio.com/map/Asheville/Cullowhee (last visited Apr. 9, 2021).

[39] For example, a taxi between Phillipston and Worcester could cost approximately $110 one way, or $220 round-trip. *See* Taxi Fare Finder, https://www.taxifarefinder.com/ (last visited Apr. 12, 2021) (searching for "Phillipston, Massachusetts," to "Worcester, Massachusetts," and selecting "Cheapest" filter).

[40] *See, e.g.*, Bearak et al., *supra* note 29 (majority of women of reproductive age in North Dakota and Wyoming and one in five women in Alaska, Idaho, Kansas, Missouri, Montana, New Mexico, and South Dakota lived more than 100 miles from the nearest provider).

approximately 125 miles each way to reach a provider in Phoenix, AZ,[41] or Dalhart (Dallam County), TX, who must travel 200 miles each way to Lubbock, TX.[42] In extreme cases, such as for patients living in Hawai‘i or in other states with island populations (such as Alaska, Maine, North Carolina, and Florida), air travel may be required to access in-person abortion care. For example, in Hawai‘i, I understand that there are no clinics offering abortion care on the islands of Kaua‘i, Hawai‘i, Lana‘i, Moloka‘i, and Ni‘ihau, necessitating inter-island travel to O‘ahu to reach the nearest abortion provider. Since these arrangements are often made within a short timeframe, the costs tend to be higher than for long-planned travel. For example, the lowest round-trip ticket to O‘ahu (bought for travel within two weeks of purchase) was $178 for Kona, Lihu’e, or Hilo, according to Kayak.com.[43] On top of flight costs, abortion patients would also need to pay for ground transportation to and from the airport and/or overnight parking. For those living on Hawai‘i, the price of a taxi to or from the Hilo airport can run from $12 for people living in Hilo to $104 for

[41] Approximately 2 hours by car or bus ($56–62 round-trip, depending on how many days in advance of travel reservation is made, with only 4:00 a.m. departures and 10:30 p.m. returns available). *See Book A Trip*, Greyhound, https://www.greyhound.com/en (last visited Apr. 11, 2021). Clinics in El Centro, CA, and Coachella, CA, are similar distances by car, but options by bus take much longer and are more expensive.

[42] Approximately 3 hours by car. There is no bus service directly from Dalhart. Patients would have to arrange transportation to Dumas, TX (approximately 35 miles away), for bus service to Lubbock (at least 3.5–5 hours, depending on schedule), at a total round-trip cost of $200–280, including a taxi from Dalhart to Dumas. *See* Greyhound, *supra* note 41; Rome2Rio, https://www.rome2rio.com/map/Dalhart/Lubbock (last visited Apr. 11, 2021).

[43] Kayak.com, http://www.kayak.com (last visited April 7, 2021).

people living in Honoka‘a.[44] Additionally, the cost of public transportation once on O‘ahu is $5.50 per day. Thus, for a woman from Honoka‘a traveling to Honolulu for abortion care, the cost of ground transportation alone (in both places) can exceed $219.[45] In addition, for many low-income women, particularly those for whom English is a second language and/or non-citizens, air travel may pose psychological and emotional hurdles, as it requires security checks, identification that may not be regularly needed, and simply the unfamiliarity of airplane travel.

28. Finally, for those who have to travel long distances or inter-island—such as patients in Hawai‘i, Buffalo (Dallas County), MO (320 miles round-trip to Kansas City, KS), or Dalhart, TX (400 miles round trip to Lubbock)—travel for abortion may require overnight lodging,[46] for example, because of limited bus

[44] *Taxicab*, Hawaii.gov: Hilo Int’l Airport, http://airports.hawaii.gov/ito/getting-to-from/ground-transportation/taxicab (last visited April 7, 2021). For patients with cars, the cost of parking at the Hilo airport is $15 per day. *Parking*, Hawaii.gov: Hilo Int’l Airport, http://airports.hawaii.gov/ito/getting-to-from/parking/ (last visited April 7, 2021). Like many other places in the United States, Hawai‘i has poor public transportation options, especially outside of O‘ahu, and visitors to the counties of Hawai‘i and Kaua‘i, for example, are strongly urged to rent a car or use taxis for local transportation. *See* Sheila Beal, *What are the public transportation options in Hawaii*, Go Visit Hawaii (Oct. 23, 2017), https://www.govisithawaii.com/2017/10/10/what-are-the-public-transportation-options-in-hawaii/; *Transportation Rankings*, U.S. News, https://www.usnews.com/news/best-states/rankings/infrastructure/transportation (last visited April 7, 2021) (ranking the state of Hawaii 40th in terms of transportation infrastructure).

[45] *Adult Fare*, The Bus: City and County of Honolulu, http://www.thebus.org/Fare/Adultfare.asp (last visited April 7, 2021).

[46] *See, e.g.*, Caitlin Gerdts et al., *Impact of Clinic Closures on Women Obtaining Abortion Services After Implementation of a Restrictive Law in Texas*, 106 Am. J. Pub. Health 857, 861–63 (2016) (in study of Texas abortion patients whose nearest abortion clinic had closed as a result of a 2013 law, 16% reported having to stay overnight to access abortion care).

schedules, to accommodate early morning appointments, to obtain the least expensive bus or flight ticket, or if the round-trip distance is too far to travel in a single day.[47] Such costs are typically higher if reservations must be made just a few days or weeks ahead of time. According to a discount website, the cost of lodging starts around $83 in Honolulu, $43 in Lubbock TX, and $49 in Kansas City, KS.[48]

29. Especially for women already struggling to make ends meet, the added costs and logistical burdens of arranging transportation to a REMS-certified provider can be onerous, if not insurmountable.

Missed Work

30. Traveling to pick up a pill in person at a hospital, clinic, or medical office instead of receiving it by mail at home, or traveling to a second health care facility because the provider who diagnosed a patient's pregnancy cannot write them a prescription for Mifeprex, also may interfere with patients' work schedules. Women who have to travel long distances to reach a REMS-certified prescriber may

[47] For example, there is no direct bus service out of Buffalo, MO. To reach Kansas City, KS, a patient would first need to figure out how to get to Springfield, MO, 30 miles away. From there, she could take a Greyhound bus to Kansas City, MO, and then a shuttle to Kansas City, KS, at a cost of $62–104 round-trip (depending on how many days in advance she makes the reservation), not including the cost of getting to Springfield and back. In addition, there is only one bus per day between Springfield and Kansas City, departing at 2:15 p.m., and arriving at approximately 6:00 p.m. Accordingly, she would also likely need to travel the day before her appointment and stay overnight. *See* Greyhound, *supra* note 41 (no results for "Buffalo, MO"; results for travel to Kansas City, MO, from Springfield). Alternative options from Springfield include, *e.g.*, a 4.5-hour bus at a cost of $130 round-trip to St. Louis, MO, or a 3.5-hour bus ride each way at a cost of approximately $72–96 round trip to Tulsa, OK, which would also likely require an overnight stay. *Id.*

[48] *See* Hotels.com, https://www.hotels.com/ (last visited Apr. 11, 2021).

miss multiple days of work. Especially for low-income workers, the burdens associated with arranging time off work can result in delayed care, lost income, and even threats to job security.

31. About 40% of women workers in the United States have no paid time off.[49] Among low-wage workers (the bottom 25%), 93% lack paid family leave and 49% lack paid sick leave[50]; and almost two-thirds of workers in jobs that do not require a college degree lack paid personal days.[51] For part-time workers,[52] 92% lack paid family leave, three-quarters have no paid sick leave, and two-thirds lack any paid vacation or holidays.[53] For those without paid time off, any time away from work in order to access abortion care translates into lost wages. According to one study, the mean wages lost as a result of traveling for abortion care because of missed

[49] Cynthia Hess et al, Inst. for Women's Pol'y Res., The Status of Women in the States: 2015, at 88 (2015), https://iwpr.org/wp-content/uploads/2020/08/R400-FINAL-8.25.2015.pdf.

[50] Pronita Gupta et al., Paid Family and Medical Leave is Critical for Low-wage Workers and Their Families 1 (Dec. 2018), https://www.clasp.org/publications/fact-sheet/paid-family-and-medical-leave-critical-low-wage-workers-and-their-families.

[51] Gregory Acs & Pamela Loprest, Urb. Inst., Employers in the Low-Skill Labor Market, Brief No. 2: Low-Skill Jobs, Work Hours, and Paid Time Off 4 (2008), https://www.urban.org/sites/default/files/publication/32211/411802-Low-Skill-Jobs-Work-Hours-and-Paid-Time-Off.PDF.

[52] Twenty-five percent of women workers are employed in a part-time position. *Economics Daily: Percentage of Employed Women Working Full Time Little Changed Over Past 5 Decades*, U.S. Bureau of Lab. Statistics (Dec. 1, 2017), https://www.bls.gov/opub/ted/2017/percentage-of-employed-women-working-full-time-little-changed-over-past-5-decades.htm?view_full.

[53] Gupta, *supra* note 50, at 1; Hess et al, *supra* note 49, at 89.

work was $198 nationally.[54]

32. Missing one or more days from work not only means lost wages, but may also put the job itself at risk, leading to economic instability. In many cases, low-wage workers have unpredictable hours or are required as a condition of employment to regularly work overtime, both of which make it difficult to reliably plan appointments and related travel during non-work hours. It can be extremely difficult for low-wage workers to get a particular day off, particularly on short notice. And taking unapproved time off to keep an appointment or travel for abortion care can cost a patient her job.

33. Furthermore, some jobs that provide sick leave or paid leave may nonetheless require documentation of the reason for the leave. Women reluctant to disclose their abortions to their employers may therefore be unable to use paid or unpaid leave, even if their employer technically provides it; and those who do disclose their reason may have the request denied by a hostile employer or be vulnerable to retaliation as a result of their abortion.

Child Care

34. As noted, approximately 60% of women seeking an abortion have at least one child.[55] Consequently, traveling for an abortion, or making an unnecessary

[54] Rachel K. Jones et al., *At What Cost? Payment for Abortion Care by U.S. Women*, 23 Women's Health Issues e173, e174 (2013), https://www.ncbi.nlm.nih.gov/pubmed/23660430.

[55] *CDC Abortion Surveillance*, *supra* note 12, at Table 7.

or additional trip to a health care facility in order to obtain an abortion, may require child care arrangements, including when the abortion patient is the child's primary caregiver, or when the time needed for the appointment and travel to and from does not align with the child or children's regular childcare or school hours.

35. Child care costs can take up a significant proportion of a low-wage worker's income. In Hawai'i, costs range from $372 per month for part-time child care for a school-aged child to $589 per month for full-time infant care. Among the largest cities in the eight representative states analyzed above, full-time monthly child care for a preschooler ranges from $973 in Kansas City, MO (Jackson County), to $2,509 in Boston, MA. In rural counties across these states, a preschooler's full-time child care ranges in cost from $471 in Dallas County, MO, to $1,047 in Sandisfield, MA. Altogether, child care for just one preschooler ranges from 17% to 28% of the monthly needs budget across these eight states, averaging 21% of the budget.

36. But the daily rate for emergency short-term child care is often even greater than the daily rate for a month- or year-long slot. In addition, because many child care options, such as at a center or family home, are only available during regular daytime work hours, if a patient must be away overnight, the costs of child care are considerably higher. And if a woman cannot find or afford paid child care that aligns with her appointment and travel time, she may need to turn to a friend,

family member, or neighbor—which may require disclosing the reason she will be away, impinging on her privacy.

The Consequences of Attempting to Pay for Abortion-Related Travel

37. As detailed above, the total out-of-pocket costs involved in accessing abortion care can be substantial compared to income. For more than half of women attaining an abortion in a multi-state 2014 study, out-of-pocket costs (not including lost wages) averaged more than one-third of their personal monthly income.[56] In order to pay for these costs, low-income patients often end up making economic trade-offs that, as noted above, can carry serious consequences for their health, safety, and long-term economic stability.[57]

38. Indeed, a 2016 study concluded that two-thirds of women find it difficult or very difficult to pay for an abortion, and that doing so prevented or delayed nearly half of abortion patients from paying for at least one other basic need, including bills, food, rent, child care, and medical care.[58] Diverting funds from other basic needs in order to access an abortion can lead to additional costs and serious consequences. For instance, if a patient diverts any amount of rent funds and

[56] Roberts et al., *supra* note 6, at e211, e214.

[57] *Id.* at e216.

[58] Deborah Karasek & Sarah C.M. Roberts, *Abortion Patients' Experience and Perceptions of Waiting Periods: Survey Evidence before Arizona's Two-visit 24-hour Mandatory Waiting Period Law*, 26 Women's Health Issues 60, 63 (2016), https://www.whijournal.com/article/S1049-3867(15)00161-9/fulltext.

therefore cannot pay her full rent, she and her family risk eviction. Other consequences of having to divert funds include utility cut-offs, having to rely on food pantries or food banks, skipping meals, missing car payments, forgoing needed medical or dental care, or losing a scarce spot in a child care program.[59] Each of these in turn can lead to major long-term harms such as job loss, food insecurity, and medical harm.[60]

39. The most common source of money for an abortion is from the man involved in the pregnancy.[61] But borrowing from a partner can be problematic for some women, particularly where the relationship itself is unhealthy. The disclosure that results from the need for resources to cover travel and other costs (as well as

[59] Sandra S. Butler & Luisa S. Deprez, *The Parents as Scholars Program: A Maine Success Story*, 17 Me. Pol'y Rev. 40 (2008), http://digitalcommons.library.umaine.edu/mpr/vol17/iss1/7.

[60] Insurance does not change this calculus. Approximately two-thirds of the states restrict Medicaid coverage for abortion. Alina Salganicoff et al., *Coverage for Abortion Services and the ACA*, Kaiser Family Found. (Sept. 19, 2014), https://www.kff.org/womens-health-policy/issue-brief/coverage-for-abortion-services-and-the-aca/. Even in the states that do provide such coverage, many low-income women cannot access it because, for example, the income-eligibility threshold is too low, they are undocumented, or the time necessary to enroll will delay their abortion care beyond the time when they can access a medication abortion. *See* Kaiser Family Found., Health Care Coverage for Immigrants (2020), https://www.kff.org/racial-equity-and-health-policy/fact-sheet/health-coverage-of-immigrants/. A multi-state 2014 study found that nearly one-third of patients who appeared eligible for Medicaid coverage based on income and state of residency did not use Medicaid to pay for their abortions. Roberts et al., *supra* note 6, at e216. Many private or marketplace plans do not cover abortion either. Salganicoff et al., *supra*. Given this and other barriers, the same 2014 study found that only one in four patients with private insurance had their abortion covered by insurance. Roberts et al., *supra* note 6, at e216. And, the pandemic has increased the number of households that have lost health insurance coverage due to job loss and the associated loss of employer-provided health insurance. Furthermore, even for those who have coverage, Medicaid and private insurance do not cover other travel-related costs, such as meals, child care, and lost wages.

[61] Jones et al. (2013), *supra* note 54, at e177.

assistance with the travel itself) may increase the risk of domestic violence,[62] a widespread problem across the country.[63]

40. Other tactics to raise funds carry their own risks and consequences. Borrowing money from a payday lender or credit card company can help pay for an emergency expense, but repaying such loans may result in a cycle of refinancing, with additional fees and compounding interest leading to increasing debt.

41. Monetary costs alone do not fully capture how disruptive having to travel for abortion care can be. At each step, from arranging care for children, to informing supervisors or coworkers, to securing transportation and lodging, to obtaining resources (whether borrowed or diverted from other needs), the psychological harm increases and the circle of people aware of the reason for travel widens, breaching patient privacy, putting relationships or employment at risk, and increasing the risk of domestic violence.[64]

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[62] Sarah CM Roberts, *Risk of Violence from The Man Involved In Pregnancy After Receiving or Being Denied An Abortion*, BMC Med. 12:144 (2014), at 1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4182793/.

[63] *See id.*; Ctrs. for Disease Control & Prevention, The National Intimate Partner and Sexual Violence Survey: 2015 Data Brief – Updated Release 2, 8 (2018) https://www.cdc.gov/violenceprevention/pdf/2015data-brief508.pdf (reporting that 43% of U.S. women had experienced some form of sexual violence in their lifetime, one in four experienced contact sexual violence, physical violence, or stalking by an intimate partner, and one in five experienced rape or attempted rape).

[64] Jill Barr-Walker et al., *Experience of Women Who Travel for Abortion: A Mixed Methods Systematic Review*, PLOS ONE 14(4), at 18 (2019), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0209991 ("Participants discussed how the need to secure time off of work, arrange childcare, or borrow money for travel

C. Research Confirms That Increased Travel to Obtain an Abortion Delays or Blocks Care

42. An extensive body of research supports the analysis above, documenting that the burdens and costs associated with traveling for abortion care delay or prevent patients from accessing care, decrease confidentiality, and increase the likelihood of anti-abortion stigma from employers, families, and/or friends.[65]

43. Research confirms that the greater the distance a patient must travel to access abortion, the less likely that the abortion will occur. For instance, a 2017 study evaluating the impact of a 2013 law that closed 24 of 41 abortion clinics in Texas—and thus increased the distance to the nearest clinic for many Texas women—found that the number of abortions declined 17% across the state between 2012 and 2014.[66] The magnitude of the decline in abortion rates increased more substantially as the distance from a patient's county of residence to the nearest abortion clinic increased: when the change in distance to an abortion clinic was 25–49 miles, abortions decreased 25.3%; when the change was 50–99 miles, abortions decreased by 35.7%; and when the change was 100 miles or more, abortions decreased by 50.3%.[67]

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or the procedure necessitated disclosing their decision to have an abortion to people at work and in their personal lives.").

[65] *Id.* at 2 (summarizing findings of multiple studies).

[66] Daniel Grossman et al., *Change in Distance to Nearest Facility and Abortion in Texas, 2012 to 2014*, 317 JAMA Network 437, 437–38 (2017), http://sites.utexas.edu/txpep/files/2017/10/Grossman-et-al-HB2-Change-in-Distance-Abortion-JAMA-2017.pdf.

[67] *Id.* at 438.

44. Other studies have documented this same inverse relationship between travel distance and abortion rates even for relatively short increases in distance. In Washington state, when a decline in the number of abortion providers led to a 12 mile increase in travel distance for rural women, the abortion rate among that population decreased by 27%.[68] In Georgia, for every 10 miles of distance from the major abortion providers in Atlanta, the number of abortions declined by 6.7 per 1,000 live births.[69] And in Ohio, when clinics in Toledo and Lima closed, necessitating greater travel distances to reach an abortion provider, abortions rates in those counties and surrounding areas dropped by 25% or more the following year.[70]

45. The research literature also shows a complex interrelationship between travel costs, distance, and delay that in turn impacts access to abortion. Travel

[68] Sharon A. Dobie et al., *Abortion Services in Rural Washington State, 1983–1984 to 1993–1994: Availability and Outcomes*, 31 Fam. Plan. Persp. 241, 241–44 (1999), https://www.guttmacher.org/sites/default/files/article_files/3124199.pdf; *see also* Robert W. Brown et al., *Provider Availability, Race, and Abortion Demand*, 67 Southern Eco. J. 656, 658 (2001) (in Texas, an increase of 10% in the travel distance from a woman's county to the nearest city with an abortion provider was associated with a 2.3% decline in the abortion rate for white women, 2.7% for African-American women, and 5.0% for Hispanic women).

[69] James D. Shelton et al., *Abortion Utilization: Does Travel Distance Matter?*, 8 Fam. Plan. Persp. 260, 260–62 (1976), https://jstor.org/stable/pdf/2134397.pdf?seq=1#page_scan_tab_contents (also finding a significantly greater increase in abortions in two counties distant from Atlanta after new abortion providers opened there, as compared to other counties in the state).

[70] Alison H. Norris et al., *Abortion Access in Ohio's Changing Legislative Context, 2010–2018*, 110 Am. J. Pub Health 1228, 1232 (2020) (abortion rate in rural counties disproportionately affected by clinic closures decreased more than 30% over study period).

burdens and costs can lead to delays in obtaining an abortion, which in turn can result in a patient being unable to access medication abortion or being turned away from the abortion clinic because by the time the patient is able to obtain the funds and make the necessary arrangements to get there, her pregnancy has advanced beyond the window for medication abortion care or the latest point in pregnancy at which the clinic provides services.[71] At the same time, delays can increase both the cost of the procedure (which typically increases as pregnancy advances and is greater for procedural abortion than medication abortion) and the cost of travel (for instance, if a patient must pay for lodging for a two-day procedure during the second trimester), thus causing further delay.[72] A nationwide 2014 study found that, for patients who were near a clinic's limit or were turned away because they exceeded that limit, the most cited reason for the delay was costs, for both travel and the procedure.[73] A 2010

[71] *See* Jerman et al., *supra* note 33, at 95, 98 (in qualitative study of 29 women traveling across state lines or long distances to access abortion in New Mexico and Michigan, most common consequence of travel and related barriers was "obtain[ing] abortions at later gestations than desired because of delays"); *see also* Norris et al., *supra* note 70, at 1233 (finding that patients in Ohio have abortions later in pregnancy than the national average and that this disparity increased as the number of facilities offering care in the state diminished).

[72] Jerman et al., *supra* note 33, at 100 (describing the "negative feedback loop," in which delay caused by difficulty raising money can lead to higher procedure costs and further delay); Diane Greene Foster & Katrina Kimport, *Who Seeks Abortions at or After 20 Weeks?*, 45 Persp. on Sexual & Reprod. Health 210, 214–15 (2013), https://doi.org/10.1363/4521013 (women who were 20 weeks or more pregnant reported difficulty getting to an abortion facility, spent more on travel, and experienced more delay); Norris et al., *supra* note 70, at 1233 (period of legislative and regulatory changes in Ohio that reduced access and resulted in clinic closures coincided with Ohioans being increasingly more likely to access abortion at later gestational ages).

[73] Ushma D. Upadhyay et al., *Denial of Abortion Because of Provider Gestational Age Limits in the United States*, Am. J. Pub. Health 1687, 1689 (2014), https://doi.org/10.2105/AJPH.2013.301378 (finding that 58.3% of patients turned away and 67%

study in Illinois found that "[m]any women reported substantial difficulty locating a clinic, traveling long distances and finding transportation," and that such obstacles were associated with seeking abortion care in the second rather than the first trimester.[74]

III. CONCLUSION

46. At *least* three out of four abortion patients have income that is insufficient to meet their basic needs. The costs and burdens of traveling to obtain an abortion, arranging child care, and lost wages entirely prevent some women from obtaining abortion care. Even for those able to access care, these burdens force many patients to forgo other necessary expenses for themselves and their families and put them at risk of longer-term economic insecurity. In addition, these burdens force women to disclose their abortions to a wider circle of people than would otherwise be necessary, thus exposing some women and their families to domestic violence and/or longer-term economic insecurity.

arriving just before the limit attributed their delay to "travel and procedure costs," while 29.8% cited "not knowing how to get to a provider"; for first trimester patients, travel and procedure cost was the second-most cited reason, after "not recognizing pregnancy").

[74] Jessica W. Kiley et al., *Delays in Request for Pregnancy Termination: Comparison of Patients in the First and Second Trimesters*, 81 Contraception J. 446, 449 (2010), https://doi.org/10.1016/j.contraception.2009.12.021.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed in Friday Harbor, WA on April 12, 2021.

Diana M. Pearce

Diana M. Pearce, Ph.D.

Pearce Decl.

Appendix

APPENDIX: Comparison of Basic Needs Budgets in Eight States With Poverty Rates Close to National and Regional Averages

State Selection Methodology: To select states for this analysis, I used states that had poverty rates closest to the national and regional averages, according to U.S. Census Bureau data, and for which current Self-Sufficiency Standard data was available. State poverty rates and the national poverty rate refers to the latest two-year average (2018–19) provided by the Census Bureau.[1] To calculate regional averages, states were grouped by Census region: Northeast, Midwest, South, and West. The average regional percentage was then calculated using the state poverty rates for all states within that region. Finally, each state's percentage below-poverty was compared to the national average and the regional average, respectively, to determine the state or states closest to each average. If 2021 Self-Sufficiency Standard data was not available for the state with the closest rate to the national or regional average, the second-closest was used instead.

State Needs Budgets: For each state, I compared the Standard (*i.e.*, needs budget) for a family with one adult and one preschooler to the local or state minimum wage for (a) the county with the largest city; (b) the county with the median Standard in the state; and (c) the county with the lowest Standard in the state. The Standard was then compared to the minimum wage for each locality, assuming full-time work. Wherever possible, the cost of a given need in the Standard is based on the amount of financial assistance that the government (federal or state) has deemed minimally adequate for that basic need (such as housing, child care, or food expenses):

- Housing: maximum rent allowed for Section 8 voucher (housing assistance) recipients as set by the U.S. Department of Housing and Urban Development
- Child care: maximum amount set by the state for reimbursement for those receiving child care assistance (minus copayments)
- Food: the U.S. Department of Agriculture's "Low-Cost" Food Plan, which covers *only* the cost of basic groceries, without any take-out or restaurant food
- Transportation: cost of a monthly pass for local public transportation, or (if no adequate option) average cost of a private car, assuming use to/from work and one weekly shopping trip, based on national data such as U.S. Highway Administration's National Household Travel Survey, and U.S. Bureau of Labor Statistics' Consumer Expenditure Survey
- Health care: assuming employer-sponsored insurance and out-of-pocket costs based on the Medical Panel Survey, the most complete national source for health and insurance costs
- Miscellaneous: 10% of all other costs, and accounting only for essentials such as clothing, nonprescription medicines, and personal hygiene items, and not including any recreation, entertainment, savings, or debt repayment
- Taxes: federal and state income tax, payroll taxes, and state and local taxes (if applicable), and accounting for federal and applicable state tax credits

[1] *Income and Poverty in the United States*, U.S. Census Bureau, at Table: Percentage of People in Poverty by State Using 2- and 3-Year Averages: 2016–17 and 2018–19, https://www.census.gov/data/tables/2020/demo/income-poverty/p60-270.html (last visited Apr. 9, 2021).

National Average Poverty Rate (2018–19): 11.1%

Northeast
Average Poverty Rate (2018–19): 9.0%

	Closest to National Average			Closest to Regional Average		
	New York[2]			**Massachusetts[3]**		
	Largest city (Queens County)[4]	Median (Schoharie County)	Least expensive (Cattaraugus County)	Largest city (Boston)	Median (Phillipston)	Least expensive (Sandisfield)
Housing	$2,091	$938	$734	$2,509	$976	$1,175
Child care	$1,285	$840	$840	$1,502	$1,047	$1,047
Food	$471	$415	$371	$559	$470	$476
Transp'n	$127	$328	$315	$90	$308	$320
Health care	$535	$485	$451	$542	$534	$534
Misc.	$451	$301	$271	$520	$333	$355
Taxes	$1,469	$588	$434	$1,615	$789	$869
Earned Income Tax Credit	$0	$0	-$75	$0	$0	$0
Child Care Tax Credit	-$50	-$50	-$58	-$50	-$50	-$50
Child Tax Credit	-$167	-$167	-$167	-$167	-$167	-$167
Monthly Self-Sufficiency Standard	$6,212	$3,678	$3,116	$7,120	$4,240	$4,559
Minimum Wage	$15.00	$12.50	$12.50	$13.50	$13.50	$13.50
Ratio (Self-Suff. to Min. Wage)	**2.4**	**1.7**	**1.4**	**3.0**	**1.8**	**1.9**

[2] The Northeastern state closest to the national average was Maine (11.0%), but current Standard data for Maine is not available. The second-closest to the national average was New York (11.8%).

[3] The Northeastern state closest to the national average was Rhode Island (9.0%), but current Standard data for Rhode Island is not available. The second-closest to the regional average was Massachusetts (8.1%). Standard data in Massachusetts is grouped by town, not county, because towns are the more meaningful local geographic unit under Massachusetts's government structure.

[4] The largest city in New York (New York City) spans multiple counties; of those, Kings County is the most populous, but its Standard data is divided into two sub-regions to capture cost variations within the county. Queens County, the second-largest, has county-wide Standard data and is used instead for ease of comparison.

Midwest
Average Poverty Rate (2018–19): 9.7%

	Closest to National Average			losest to Regional Average		
	Missouri[5]			**Illinois[6]**		
	Largest city (Jackson County)	Median (Adair County)	Least expensive (Dallas County)	Largest city (Cook County)	Median (Jersey County)	Least expensive (Pike County)
Housing	$973	$662	$662	$1,197	$791	$700
Child care	$782	$486	$471	$1,179	$647	$547
Food	$388	$347	$378	$384	$380	$358
Transp'n	$352	$331	$337	$100	$275	$266
Health care	$603	$720	$646	$446	$594	$565
Misc.	$310	$255	$249	$331	$269	$244
Taxes	$739	$443	$418	$857	$600	$473
Earned Income Tax Credit	$0	-$95	-$110	$0	-$41	-$137
Child Care Tax Credit	-$50	-$60	-$63	-$50	-$55	-$63
Child Tax Credit	-$167	-$167	-$167	-$167	-$167	-$167
Monthly Self-Sufficiency Standard	$3,929	$2,922	$2,823	$4,277	$3,293	$2,787
Minimum Wage	$10.30	$10.30	$10.30	$13.00	$11.00	$11.00
Ratio (Self-Suff. to Min. Wage)	**2.2**	**1.6**	**1.6**	**1.9**	**1.7**	**1.5**

[5] Missouri's 2018–19 average poverty rate was 10.8%, the closest to the national average among Midwestern states.

[6] Illinois's 2018–19 average poverty rate was 9.8%, the closest to the regional average for Midwestern states.

South
Average Poverty Rate (2018–19): 13.2%

	Closest to National Average **Texas**[7]			Closest to Regional Average **North Carolina**[8]		
	Largest city (Harris County)	Median (Dallam County)	Least expensive (Uvalde County)	Largest city (Mecklenburg County)	Median (Jackson County)	Least expensive (Person County)
Housing	$1,129	$762	$734	$1,237	$718	$757
Child care	$788	$665	$509	$1,053	$688	$521
Food	$376	$374	$296	$435	$397	$375
Transp'n	$355	$311	$318	$301	$270	$276
Health care	$637	$683	$682	$495	$607	$454
Misc.	$329	$279	$254	$352	$268	$238
Taxes	$606	$458	$367	$880	$543	$405
Earned Income Tax Credit	$0	-$39	-$111	$0	-$47	-$136
Child Care Tax Credit	-$50	-$55	-$63	-$50	-$58	-$65
Child Tax Credit	-$167	-$167	-$167	-$167	-$167	-$161
Monthly Self-Sufficiency Standard	$4,004	$3,272	$2,820	$4,536	$3,219	$2,664
Minimum Wage	$7.25	$7.25	$7.25	$7.25	$7.25	$7.25
Ratio (Self-Suff. to Min. Wage)	**3.2**	**2.6**	**2.2**	**3.6**	**2.6**	**2.1**

[7] The Southern state closest to the national average was Oklahoma (12.1%), but current Standard data for Oklahoma is not available. The second-closest to the national average was Texas (12.4%).

[8] North Carolina's 2018–19 average poverty rate was 12.9%, the closest to the regional average for Southern states.

West
Average Poverty Rate (2018–19): 10.2%

	Closest to National Average **California**[9]			Closest to Regional Average **Arizona**[10]		
	Largest city (Los Angeles County)	Median (Riverside County)	Least expensive (Modoc County)	Largest city (Maricopa County)	Median (La Paz County)	Least expensive (Santa Cruz County)
Housing	$2,058	$1,417	$807	$1,259	$952	$788
Child care	$1,447	$1,054	$757	$879	$630	$700
Food	$448	$408	$435	$408	$396	$334
Transp'n	$342	$340	$323	$269	$241	$241
Health care	$507	$511	$849	$518	$624	$484
Misc.	$480	$373	$317	$333	$284	$255
Taxes	$1,145	$727	$571	$688	$524	$399
Earned Income Tax Credit	$0	$0	$0	$0	-$15	-$103
Child Care Tax Credit	-$50	-$50	-$50	-$50	-$53	-$63
Child Tax Credit	-$167	-$167	-$167	-$167	-$167	-$167
Monthly Self-Sufficiency Standard	$6,210	$4,613	$3,842	$4,138	$3,417	$2,868
Minimum Wage	$15.00	$14.00	$14.00	$12.15	$12.15	$12.15
Ratio (Self-Suff. to Min. Wage)	**2.4**	**1.9**	**1.6**	**2.0**	**1.6**	**1.4**

[9] California's 2018–19 average poverty rate was 11.0%, the closest to the national average among Western states.

[10] The Western state closest to the regional average was also California (11.0%). The second-closest was Arizona (11.4%).

Suppl. Ex. D

Letter from Soc'y of Family Planning to Christine Nguyen, MD (Aug. 13, 2021)

Society of Family Planning & SFP RESEARCH FUND

August 13, 2021

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Urology, Obstetrics, and Gynecology
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: US Food and Drug Administration's review of the risk evaluation and mitigation strategy for mifepristone

Dear Dr. Christine Nguyen:

On May 7, 2021, the US Food and Drug Administration (FDA) announced a review of the risk evaluation and mitigation strategy for the drug mifepristone (hereafter, the mifepristone REMS). On behalf of the Society of Family Planning, the academic society for Complex Family Planning subspecialists and over 1,000 academicians, scientists, and partners focused on abortion and contraception research and clinical care, we write to share relevant evidence to support your review of the mifepristone REMS. We appreciate the opportunity to lend the expertise of the Society and its members to this process and applaud your efforts, as a science-based agency, to center sound medical evidence in the decision-making process related to mifepristone and its distribution and use.

As the organization representing Complex Family Planning Fellowship-trained obstetrician-gynecologists—the leaders in clinical care and medical education related to complex abortion and contraception—we conclude the additional controls provided by the REMS are not medically necessary to ensure patient safety. Our 30 years of experience within the Fellowship providing abortion and pregnancy loss care in complex cases, as well as the existing evidence on this topic described in detail below, does not support requiring provider certification and registration to prescribe mifepristone or restricting the healthcare professionals that can prescribe mifepristone. Mifepristone is extremely safe and highly effective when provided via a health center, pharmacy, or home delivery, and does not require a clinician to oversee dispensing.

On behalf of our expert membership, we offer the following summary of peer-reviewed scientific evidence related to the mifepristone REMS, with a focus on research published since the most recent FDA-approved labeling change in 2016. **We conclude that the current REMS, specifically the provisions that require provider certification and registration and restrict where mifepristone may be dispensed, confers no benefit in terms of safety, efficacy, or acceptability of the drug mifepristone and instead creates barriers to use that negatively impact public health and equity in access to care.**

Requiring provider certification and registration to prescribe mifepristone is unnecessary because it does not increase patient safety and constrains abortion provision.

- **The mifepristone REMS currently requires that providers are specially certified to prescribe the drug and must register as prescribers directly with the manufacturer(s); however, there is no evidence this requirement increases abortion safety**. In Canada, mifepristone-specific requirements for provider certification were lifted in November 2017. According to a comprehensive analysis of linked medical and financial records in Ontario, medication abortion remained extremely safe after deregulation, with a major complication rate of 0.33% compared to a rate of 0.31% in an analysis of a similar administrative dataset from California under the REMS, and consistent with a clinical review finding major complication rates <1% across multiple studies of mifepristone use for early abortion.[1–3]

- **Requiring provider certification and registration prevents many providers from incorporating mifepristone into their scope of practice**. In a representative national population-based survey of obstetrician-gynecologists, Grossman and colleagues found that 28% of obstetrician-gynecologists who did not currently provide care using mifepristone would do so if they could prescribe it similarly to other drugs.[4] Several recent, rigorous qualitative studies with diverse groups of clinicians have also demonstrated how the REMS creates barriers to incorporation of mifepristone into practice by creating administrative burdens that clinical champions are unable to overcome.[5,6]

The current restrictions on where mifepristone may be dispensed are unnecessary because mifepristone dispensing in clinical care settings is not associated with higher efficacy, greater safety, or greater acceptability compared to dispensing in brick-and-mortar pharmacies or via postal mail or delivery service.

- **The requirement for in-person dispensing of mifepristone in certain health care settings confers no safety benefit**. Through the mifepristone labeling change approved in 2016, the FDA recognized that requiring misoprostol be administered in clinical settings as part of early abortion care is unnecessary. As the summary of the peer-reviewed literature below suggests, patient self-administration of mifepristone at home is effective, safe, and acceptable. However, the current mifepristone REMS further require that mifepristone be distributed “only in…clinics, medical offices, and hospitals.”

- **Mifepristone can be safely dispensed in brick-and-mortar pharmacies**. Pharmacists are well qualified to assure safe dispensing of medications with a comparable safety profile to the 200 mg mifepristone tablet, including the 300 mg formulation of mifepristone for Cushing’s syndrome, which is not subject to a REMS. Evidence from high-income countries with health care infrastructure comparable to the US has demonstrated the acceptability of pharmacy dispensing of mifepristone. For example, mifepristone is currently distributed by pharmacists in Canada, a practice that Canadian physicians report facilitates the provision of medication abortion with mifepristone.[7] In the

US, physicians support pharmacy dispensing of mifepristone. In a qualitative study of primary care providers' perceptions of and experiences with mifepristone, Rasmussen and colleagues found that primary care providers in Illinois support pharmacy dispensing of mifepristone, describing it as a more patient-centered approach to administration of this drug.[8] Further, a recent US study demonstrated that pharmacy dispensing of mifepristone is safe and effective. In a study that included eight pharmacies in California and Washington state, Grossman and colleagues demonstrated that mifepristone dispensing by pharmacists in the pharmacy setting after the patient received counseling from a clinician is as effective (93.5% abortion completion with medication alone) as in-clinic dispensing efficacy reported by Winikoff and colleagues in a large multi-site national trial.[9,10] In Grossman and colleagues' study, only three (1.3%) participants visited an emergency department during the study follow up period, a lower proportion than most clinical trials of medication abortion using in-clinic mifepristone administration (range 2.9-4.1%).[10,11]

- **Mifepristone can also be safely dispensed by mail**. In a large (N=1,157 abortions) national US-based clinical trial of mifepristone dispensing by mail (the Teleabortion study), Chong and colleagues also found that mifepristone dispensing by direct mail to consumers is effective (95% abortion completion with medication alone), with only 0.9% experiencing any serious adverse event compared to an adverse event rate of 0.65% in a large (N=233,805 medication abortions) retrospective cohort study of in-clinic mifepristone administration.[12,13]

- **Retrospective analyses of rapid practice adaptations in the context of the COVID-19 pandemic further demonstrate the safety, efficacy, and acceptability of mifepristone dispensing by mail**. In a large (N=52,218) retrospective cohort study, Aiken and colleagues reported on the safety, efficacy, and acceptability of telemedicine abortion at Britain's largest abortion providers, which rapidly adapted to provide medication abortion using telemedicine during the spring and summer of 2020.[14] Following a telehealth consultation, individuals with a last menstrual period dating the pregnancy up to 69 days and without symptoms of ectopic pregnancy were able to receive both mifepristone and misoprostol for home administration. Investigators found that while medication abortion was equally effective in the telemedicine model (98.8%) vs the traditional in-clinic mifepristone administration model (98.2%, p=1.0), individuals using telemedicine had a shorter wait time between first contact and initiating the medication abortion (6.5 days vs. 10.7 days, p<0.001).

- **Whether patients receive mifepristone at a pharmacy or by mail, they report high acceptability**. In their pharmacy dispensing study, Grossman and colleagues report that 74.3% of patients would recommend pharmacy dispensing of mifepristone to a friend in a similar situation, and 65.4% were highly satisfied with their abortion experience.[9] Hyland and colleagues report that 97% of women cared for by an Australian telemedicine medication abortion service report high satisfaction, and Chong and colleagues report that 85% of participants in the Teleabortion study found their abortion experience "very satisfactory".[12,15]

Requiring provider certification and registration to prescribe mifepristone and mifepristone dispensing restrictions may lead to abortions happening later in pregnancy. Unfortunately, abortions become more socially and clinically complicated the further along in a pregnancy the abortion occurs.[2,16–18] Thus, restrictions such as the mifepristone REMS that limit people's ability to access abortion as soon as they discover they are pregnant negatively impact public health. Delays are particularly problematic for people with low incomes as abortions after the first trimester are more expensive and often result in even further delays in obtaining a desired abortion.[19–21] In Canada, where abortions are covered as part of universal health care, the proportion of abortions in the second trimester decreased by approximately 12% after mifepristone deregulation.[1] In the US, where limited access and cost are major contributors to delays in abortion, lifting the REMS may result in an even greater shift in abortions to earlier gestational ages.

The National Academies of Science, Engineering, and Medicine defines quality abortion care as safe, effective, patient-centered, timely, efficient, and equitable.[16] **By unnecessarily limiting the number of mifepristone providers in the US, the mifepristone REMS adversely impacts timeliness and equity in access to care.** As the academic society representing Complex Family Planning subspecialists, scientists, and partners focused on abortion and contraception research and clinical care, we hope this sound medical evidence is held central in your review of the mifepristone REMS. We appreciate your commitment to centering science and ensuring that policy decisions are based on the latest evidence.

Sincerely,

The Society of Family Planning Board of Directors

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Suppl. Ex. E

Risk Evaluation & Mitigation Strategy (REMS) Single Shared System for Mifepristone (2023)

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.

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]

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

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.**

Suppl. Ex. F

Letter from Maureen G. Phipps, MD, MPH, FACOG, Judette Louis, MD, MPH, and Matt J. Granato, LLM, MBA, to Stephen M. Hahn, MD (Apr. 20, 2020)

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

April 20, 2020

Stephen M. Hahn, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue NW
Silver Spring, MD 20993

Re: Docket Number: FDA-2020-D-1106; Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals

Dear Commissioner Hahn:

On behalf of more than 60,000 of the nation's primary care obstetrician-gynecologists and subspecialty and high-risk obstetric practitioners dedicated to advancing women's health, thank you for your recent action to suspend enforcement of Risk Evaluation and Mitigation Strategy (REMS) requirements for certain drugs with laboratory testing or imaging requirements for the duration of the COVID-19 public health emergency. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine urge the U.S. Food and Drug Administration (FDA) to immediately expand this policy to REMS and Elements to Assure Safe Use (ETASU) requirements for certain prescription drugs requiring in-person health care professional administration, where treatment could safely occur through telehealth or self-administration. In addition, physicians who provide such services in accordance with current clinical guidelines during this pandemic should not be held liable.

Obstetrician-gynecologists are serving on the front lines responding to the COVID-19 crisis. In order to provide the safest care for their patients and themselves, in-person visits are limited to emergency and essential physically necessary visits. We support the FDA's acknowledgment that REMS-required health care professional in-person dispensation is difficult because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. Under these circumstances, undergoing in-person clinic administration in order to obtain a drug subject to a REMS can put patients and others, including health care professionals and their families, at risk for COVID-19 transmission. As referenced in ACOG Committee Opinion #798, *Implementing Telehealth in Practice*, evidence suggests that telehealth provides comparable health outcomes when compared with traditional methods of health care delivery without compromising the patient–physician relationship.[1] Telehealth has quickly become integrated into nearly every aspect of obstetrics and gynecology. During this pandemic, it is essential to use telehealth services to limit COVID-19 transmission.

It is critical that the FDA promptly expand its recent policy to apply to the REMS and ETASU requirements for certain drugs requiring in-person dispensation, especially mifepristone. The current REMS and ETASU requirements for mifepristone are outdated and serve as a barrier to accessing this safe, effective medication. Further, they cause unnecessary delays in obtaining time-sensitive health care, without supporting improvements to patient safety or outcomes. During this federally declared public health emergency, these antiquated and superfluous requirements put patients and their physicians at risk, with no demonstrated benefit. As noted in the ACOG Position Statement, *Improving Access to*

Mifepristone for Reproductive Health Indications, mifepristone has been used by over 3 million women in the United States since FDA approval in 2000 and strong evidence exists regarding the safety of mifepristone for medication-induced abortion and medical management of early pregnancy loss.[2,3,4,5]

Restricting access to mifepristone interferes with the ability of obstetrician–gynecologists and other women's health clinicians to deliver the highest quality care for their patients, especially during the COVID-19 pandemic. Abortion is an essential component of comprehensive health care and is a time-sensitive service for which a delay of several weeks, or in some cases days, may increase the risks or potentially make it completely inaccessible.[6] Temporarily waiving REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals is particularly important for patients who suffer from other medical conditions and are at higher risk of serious complications from COVID-19, as well as those in rural areas for whom hours of travel for in-person administration would disallow social distancing recommendations and travel advisories.

In addition, we urge you to consider waiving the requirement for health care professional administration of subcutaneous depot medroxyprogesterone acetate (DMPA). Several studies have shown patient interest in self-administration and increased continuation of DMPA via subcutaneous at-home delivery.[7,8,9] In a period when limiting patient interactions with the health care system is essential to prevent COVID-19 transmission, it is in our patients' best interest to have unencumbered access to the contraceptive method of their choice, including DMPA.

Ensuring the safety of patients and physicians during the COVID-19 pandemic requires policy changes such as those already enacted by FDA to waive the REMS requirements for certain drugs with laboratory testing or imaging requirements. We strongly urge FDA to further protect patients and their health care professionals from the risk of transmission by promptly expanding the existing policy to waive REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals. Thank you for your consideration. We are available to answer any questions you may have regarding these issues.

Sincerely,

Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists

Judette Louis, MD, MPH
President
Society for Maternal-Fetal Medicine

Matt J. Granato, LL.M., MBA
Chief Executive Officer
Society for Maternal-Fetal Medicine

[1] Implementing telehealth in practice. ACOG Committee Opinion No. 798. American College of Obstetricians and Gynecologists. Obstet Gynecol 2020;135:e73–9.
[2] Improving Access to Mifepristone for Reproductive Health Indications. Position Statement. American College of Obstetricians and Gynecologists. June 2018. Available at https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications.
[3] Cleland K, Smith N. Aligning mifepristone regulation with evidence: Driving policy change using 15 years of excellent safety data. *Contraception*. 2015;92(3):179-181. doi:10.1016/j.contraception.2015.06.016.
[4] Sixteen Years of Overregulation: Time to Unburden Mifeprex. *N Engl J Med*. 2017;376(8):790-794.
[5] Song LP, Tang SY, Li CL, Zhou LJGYK, Mo XT. Early medical abortion with self-administered low-dose mifepristone in combination with misoprostol. *J Obstet Gynaecol Res*. 2018;44(9):1705-1711. doi:10.1111/jog.13716.
[6] Joint Statement on Abortion Access During the COVID-19 Outbreak. March 18, 2020. Available at https://www.acog.org/news/news-releases/2020/03/joint-statement-on-abortion-access-during-the-covid-19-outbreak.
[7] Upadhyay UD, Zlidar VM, Foster DG. Interest in self-administration of subcutaneous depot medroxyprogesterone acetate in the United States. *Contraception*. 2016;94(4):303-313. doi:10.1016/j.contraception.2016.06.006.
[8] Kohn JE, Simons HR, Della Badia L, et al. Increased 1-year continuation of DMPA among women randomized to self-administration: results from a randomized controlled trial at Planned Parenthood. *Contraception*. 2018;97(3):198-204. doi:10.1016/j.contraception.2017.11.009.
[9] Burke HM, Chen M, Buluzi M, et al. Effect of self-administration versus provider-administered injection of subcutaneous depot medroxyprogesterone acetate on continuation rates in Malawi: a randomised controlled trial. *Lancet Glob Heal*. 2018;6(5):e568-e578. doi:10.1016/S2214-109X(18)30061-5.

Suppl. Ex. G

Letter from Maureen G. Phipps, MD, MPH, FACOG, to Janet Woodcock, MD (Oct. 6, 2021)

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

October 6, 2021

Janet Woodcock, MD
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Re: U.S. Food and Drug Administration's review of the risk evaluation and mitigation strategy for mifepristone

Dear Acting Commissioner Woodcock:

On behalf of the American College of Obstetricians and Gynecologists (ACOG), representing more than 60,000 physicians and partners dedicated to advancing women's health, we write to express our strong support for the review of the risk evaluation and mitigation strategy (REMS) for mifepristone currently underway at the U.S. Food and Drug Administration (FDA). ACOG supports efforts to improve access to quality women's health care and, given the decades of research and data reinforcing the safety of this medication, urges the FDA to remove the REMS and Elements to Assure Safe Use (ETASU) requirements for mifepristone.

Mifepristone has been used by over 3 million women in the United States since FDA approval in 2000 and robust evidence exists regarding the safety of mifepristone for medication-induced abortion.[1,2,3,4*] The REMS and ETASU requirements for mifepristone are inconsistent with those for other medications with similar safety profiles, and create barriers to access without demonstrated improvements to patient safety or outcomes. These medically unnecessary requirements restricting access to mifepristone interfere with the ability of obstetrician–gynecologists and other health care professionals to deliver the highest quality care for their patients. In addition to being supported by researchers, clinicians, and more than twenty years of data, removing the REMS and ETASU requirements for mifepristone is consistent with FDA's mission to ensure the safety and efficacy of medications and help "…the public get the accurate and science-based information they need to use medical products…"[5]

ACOG is the premier professional membership organization for obstetrician-gynecologists and produces practice guidelines for women's health clinicians based on the best available science and evidence. As referenced in ACOG Practice Bulletin 225, *Medication Abortion Up to 70 Days of Gestation*, medication abortion is a safe and effective method of providing abortion. The REMS restrictions for mifepristone do not make care safer, are not based on medical evidence or need, and create barriers to patient access to medication abortion.[6, 7, 8] Abortion is an essential component of comprehensive health care and is a time-sensitive service for which a delay of several weeks, or in some cases days, may increase the risks or

[*] Recent evidence also supports the use of mifepristone to improve the safe and effective medical management of early pregnancy loss.
See Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone pretreatment for the medical management of early pregnancy loss. N Engl J Med 2018;378:2161-70. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1715726. Retrieved July 9, 2018; and
Westhoff CL. A Better medical regimen for the management of miscarriage. N Engl J Med 2018;378:2232-3. Available at: https://www.nejm.org/doi/full/10.1056/NEJMe1803491. Retrieved July 9, 2018.

potentially make it completely inaccessible.[9] Furthermore, research conducted during the COVID-19 pandemic, when enforcement of the in-person dispensing requirement for mifepristone was suspended, demonstrates the safety of providing abortion through telehealth contact and mailed medications.[10,11] Additionally, recent data suggests that patients offered telemedicine with mailed medications had abortions earlier than those without this option.[12] Removing the REMS and ETASU on mifepristone will improve access to medication-induced abortion and enhance patient care.

ACOG is pleased that the FDA is conducting a thorough review of the REMS restrictions for mifepristone and urges the FDA to remove the medically unnecessary REMS and ETASU restrictions that hinder access to medication abortion. Thank you for your attention to this critical issue. We are available to answer any questions.

Sincerely,

Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists

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[1] Improving Access to Mifepristone for Reproductive Health Indications. Position Statement. American College of Obstetricians and Gynecologists. June 2018. Available at https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications.
[2] Cleland K, Smith N. Aligning mifepristone regulation with evidence: Driving policy change using 15 years of excellent safety data. *Contraception*. 2015;92(3):179-181. doi:10.1016/j.contraception.2015.06.016.
[3] Sixteen Years of Overregulation: Time to Unburden Mifeprex. *N Engl J Med*. 2017;376(8):790-794.
[4] Song LP, Tang SY, Li CL, Zhou LJGYK, Mo XT. Early medical abortion with self-administered low-dose mifepristone in combination with misoprostol. *J Obstet Gynaecol Res*. 2018;44(9):1705-1711. doi:10.1111/jog.13716.
[5] U.S. Food and Drug Administration. FDA Mission. Available at https://www.fda.gov/about-fda/what-we-do. Retrieved September 20, 2021.
[6] Medication abortion up to 70 days of gestation. ACOG Practice Bulletin No. 225. American College of Obstetricians and Gynecologists. Obstet Gynecol 2020;136:e31–47.
[7] Grossman D, Grindlay K, Altshuler AL, Schulkin J. Induced abortion provision among a national sample of obstetrician-gynecologists. Obstet Gynecol 2019;133:477–83.Raymond EG, Blanchard K, Blumenthal PD, Cleland
[8] Raymond EG, Blanchard K, Blumenthal PD, Cleland K, Foster AM, Gold M, et al. Sixteen years of overregulation: time to unburden mifeprex. Mifeprex REMS Study Group. N Engl J Med 2017;376:790–4.
[9] Joint Statement on Abortion Access During the COVID-19 Outbreak. March 18, 2020. Available at https://www.acog.org/news/news-releases/2020/03/joint-statement-on-abortion-access-during-the-covid-19-outbreak.
[10] Chong E, Shochet T, Raymond E, Platais I, Anger H, Raidoo S, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. Contraception 2021.
[11] Kerestes C, Murayama S, Tyson J, Natavio M, Seamon E, Raidoo S, et al. Provision of medication abortion in Hawai‘i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021.
[12] Aiken A, Lohr P, Lord J, Ghosh N, Starling J. Effectiveness, safety and acceptability of no-test medical abortion provided via telemedicine. British J Obstet Gynecol 2021.

Suppl. Ex. H

Letter from Patrizia Cavazzoni, MD, to Donna J. Harrison, MD & Quentin L. Van Meter, MD, FCP, Re: Docket No. FDA-2019-P-1534 (Dec. 16, 2021)

Donna J. Harrison, M.D.
Executive Director
American Association of Pro-Life Obstetricians and Gynecologists
P.O. Box 395
Eau Claire, MI 49111-0395

Quentin L. Van Meter, M.D., FCP
President
American College of Pediatricians
P.O. Box 357190
Gainesville, FL 32635-7190

December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

(1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:

- Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.

- Dosage and Administration:
  - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

  - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

U.S. Food & Drug Administration
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- Contraindications - Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

- Adverse Event Reporting - Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

- Additional studies - The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

(2) Retain the Mifeprex REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Mifeprex

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H), "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.[1]

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[2] Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use included: (1) prescriber certification (ETASU A); (2) that Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber

[1] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.
[2] 73 FR 16313 (Mar. 27, 2008).

(ETASU C); and (3) that Mifeprex is dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the applicant Danco Laboratories, LLC (S-020 efficacy supplement). The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective, as well as the process for follow-up after administration of the drug.

Specifically, the following changes, among others, were made as part of the 2016 approval:[3]

- Revised the dosing regimen to consist of 200 mg of Mifeprex taken by mouth, followed in 24-48 hours by 800 mcg of misoprostol taken buccally (in the cheek pouch). This differs from the originally approved dosing regimen of 600 mg of oral Mifeprex followed 48 hours later by 400 mcg of oral misoprostol.

- Revised the indication for use of Mifeprex, in a regimen with misoprostol, to extend the maximum gestational age for the medical termination of intrauterine pregnancy from 49 days to 70 days.

- Reduced the number of office visits by the patient under the approved regimen from three to one.

- Replaced the term "physician" with the term "healthcare provider."

In addition, after reviewing the data and information submitted by the applicant in the S-020 efficacy supplement, and after taking into consideration the safety data that had become available since the initial approval of Mifeprex in 2000, we determined the Mifeprex REMS continued to be necessary to ensure the benefits of the product outweigh the risks. However, we approved modifications to the Mifeprex REMS that reflected the changes approved in the efficacy supplement. These changes to the REMS included, among others:[4]

- Updating the Prescriber Agreement Form to reflect the revised indication and dosing regimen.

- Removing the Medication Guide as a REMS element (but retaining the Medication Guide as labeling).

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[3] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

[4] See https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf.

- Removing the requirement that certified prescribers report certain enumerated adverse events to the applicant (specifically, any hospitalization, transfusion or other serious adverse events), but retaining the requirement that certified prescribers report all deaths to the sponsor.

Under the March 2016 approval, the Mifeprex REMS also continued to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.[5]

B. Generic Version of Mifeprex

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). This action took place after this Petition was submitted to the Agency. As required by 21 CFR 314.94(a)(8), GenBioPro's approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex. Accordingly, although we refer to the Mifeprex labeling in several sections of this response, our discussions in this response apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.[6]

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. -1(i)). At the time we approved GenBioPro's generic version of Mifeprex, that ANDA product was required to use a single, shared system for the ETASU with the brand drug product, Mifeprex, unless the requirement was waived by FDA (21 U.S.C. 355-1(i)). FDA did not waive this requirement. Accordingly, at the same time that FDA approved GenBioPro's generic version of Mifeprex in 2019, FDA approved a supplemental new drug application (sNDA) for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In establishing the single, shared system REMS in 2019, no substantive changes were made to the ETASU in the March 2016 Mifeprex REMS. References to the REMS in this response refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

C. In-Person Dispensing Requirement During the COVID-19 PHE

[5] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf.

[6] We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone - as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

FDA has recognized that during the COVID-19[7] public health emergency (PHE),[8] certain REMS requirements for various products may be difficult to comply with because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. The Agency has also received queries concerning products with REMS that have ETASUs, including REMS with ETASUs that restrict distribution, and the impact of such ETASUs on patient access when patients self-isolate or are subject to quarantine.

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 PHE regarding the requirement in the Mifepristone REMS Program that mifepristone used for medical termination of intrauterine pregnancy through 70 days gestation be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement").

Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020 to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[9]

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

FDA's intent to exercise enforcement discretion with respect to these requirements during the COVID-19 PHE was the result of a thorough scientific review by experts within FDA's Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports.

D. Minor Modification

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[7] The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19).

[8] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[9] *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

In response to a request submitted by the applicants, FDA approved a minor modification to the Mifepristone REMS Program on May 14, 2021. This minor modification revised the Patient Agreement Form to use gender neutral language. Specifically, the pronouns "she" and "her" in the Patient Agreement Form were replaced with "the patient." The minor modification also included revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form. These changes did not affect the substance of the Patient Agreement Form, the REMS document, or the Mifepristone REMS Program.

E. Review of the Mifepristone REMS Program

In 2021, FDA also undertook a full review of the Mifepristone REMS Program.[10] In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA (together, the Applicants). As discussed in more detail below, based on our review of this information, FDA has determined that certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation; and therefore, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risk. Specifically, we find that the healthcare provider certification and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions continue to be necessary components of the REMS to ensure the benefits of mifepristone outweigh the risks for this indication.

We also find that the in-person dispensing requirement is no longer necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation. We have concluded that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added.[11] Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Accordingly, today we are sending a REMS Modification Notification letter to both Applicants in the Mifepristone REMS Program. As stated in that letter, FDA has concluded that a modification is necessary and must include the following changes:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

[10] We note that the Agency is in litigation regarding the Mifepristone REMS Program and committed to conducting a full review of the Mifepristone REMS Program, including reviewing any relevant data and evidence submitted to the Agency by the Plaintiffs in that litigation (*Chelius et al v. Becerra*, Joint Mot. to Stay Case Pending Agency Review, ECF No. 148, May 7, 2021, Civ. No. 1:17-00493 (D. Haw.)).

[11] Although we have determined that the Mifepristone REMS Program must be modified to add a requirement for pharmacy certification, this was not raised in your Petition and therefore is not discussed further in this response.

- Adding a requirement that pharmacies that dispense the drug be specially certified.

II. DISCUSSION OF ISSUES RAISED

A. Mifeprex Regimen

1. Indications and Usage

In the Petition, you ask FDA to restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to limit Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, to 49 days gestation (Petition at 1 and 3). For the reasons explained below, we deny this request.

Citing to a 2011 study and a practice bulletin issued by the American College of Obstetricians and Gynecologists (ACOG), you state that medical abortion[12] regimens demonstrate an increase in complications and failures, including serious risks of hemorrhage, infection, and ongoing pregnancy, after 49 days gestation (Petition at 3-4).

Our review of the S-020 efficacy supplement in 2016 concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.[13] Complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of Mifeprex (with an indication for medical termination of intrauterine pregnancy through 49 days gestation) were 92.1 percent and 95.5 percent in the United States and French trials, respectively.[14] The studies reviewed in support of the 2016 approval for Mifeprex (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 Clinical Review of the S-020 efficacy supplement summarized clinical outcomes and adverse effects from 22 studies (7 in the United States and 15 from outside the United States) through 70 days gestation, using the currently approved regimen of 200 mg oral mifepristone with 800 mcg buccal misoprostol. The ranges of complete medical abortion rates calculated by the clinical reviewer were 93.2 percent to 98.7 percent in the United States studies, and 92 percent to 98 percent in the non-United States studies.[15]

Serious adverse events associated with the use of mifepristone through 70 days gestational age are rare. Per the current mifepristone labeling, the rates of serious adverse events are low: transfusions are 0-0.1 percent, sepsis is less than 0.01 percent, hospitalization related to medical abortion is 0-0.7 percent, and hemorrhage is 0.1 percent.[16] As discussed

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[12] In this response, the terms "medical abortion" and "medication abortion" both refer to the use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy.

[13] See 2016 Clinical Review available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf, at 32-38 and 47-47.

[14] See 1999 Medical Officer's Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf, at 11 (Table 1) and 16.

[15] See 2016 Clinical Review, supra n. 13, at 28-31.

[16] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

throughout this response, the benefit/risk assessment supported our 2016 conclusion that the product is safe and effective through 70 days gestation.

In support of your assertion that medical abortion demonstrates an increase in complications after 49 days gestation, you cite to Mentula, et al.,[17] a register-based, retrospective cohort study that included 18,248 women in Finland who underwent medical abortion between January 1, 2003, and December 31, 2006 (Petition at 3). As an initial matter, we note that the Mentula study was primarily designed to assess the immediate adverse events following medical abortion in the second trimester (13 to 24 gestational weeks as defined by the authors) and then compare those events to those identified with medical abortion in the first trimester (up to 12 gestational weeks as defined by the authors). The study was not designed to compare rates of complications across gestational weeks within the first trimester. It is true that the Mentula publication includes information on the percentages of women who had surgical evacuation following medical abortion and the percentages of women who had infection following medical abortion, based on weekly gestational age, from 5 weeks to 20 weeks gestation.[18] However, the data in the Mentula study are relatively old (2003-2006); in our 2016 review of the S-020 efficacy supplement, we conducted an extensive review of more recent data[19] and concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.

You also cite to ACOG Practice Bulletin No. 143, which states: "the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days."[20] This statement is based on a 1998 publication which evaluated patients undergoing medical abortion with mifepristone 600 mg and then oral misoprostol 400 mcg two days later.[21] The regimen studied in this 1998 publication is not the currently approved regimen for mifepristone in the United States. Further, ACOG Practice Bulletin No. 143 has been withdrawn and replaced by Practice Bulletin No. 225, which was published in October 2020 and no longer contains this statement.[22]

You also state that the failure rate of the approved regimen (which you refer to as the "buccal misoprostol regimen") increases as the gestational age increases, especially at

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[17] Mentula MJ, Niinimake M, Suhonen S, et al. Immediate Adverse Events After Second Trimester Medical Termination of Pregnancy: Results of a nationwide registry study, Human Reproduction. 2011;26(4):927-932.
[18] Id. at Fig. 2 and Fig. 3. Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of abortion completion rates accounts for the need for surgical intervention. In clinical studies we reviewed, success of medical abortion was defined as the complete expulsion of the products of conception without the need for surgical intervention.
[19] See 2016 Cross-Discipline Team Leader Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf, at 37 (Table 4).
[20] Petition at 3. See Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.
[21] Spitz I, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United Sates, NEJM. 1998;338 (18):1241-1247.
[22] See ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. Obstetrics and Gynecology 2020; 136(4); e31 to e47.

gestational ages greater than 49 days, relying on a 2015 meta-analysis,[23] and that the gestational limit should not have been increased (Petition at 3-4). We agree that the failure rate of medical abortion regimens, including the currently approved regimen, generally increases with increasing gestational age. However, the increase in failure rate with each incremental week of gestation, as described in approved mifepristone labeling and in this 2015 meta-analysis, is small, and we believe that the benefit/risk profile for medical termination of intrauterine pregnancy between 49 and 70 days gestation remains acceptable.

For these reasons, we deny your request that FDA limit mifepristone, in a regimen with misoprostol for the termination of intrauterine pregnancy, to 49 days gestation.

2. Dosage and Administration

a. Prescriber Qualifications

You state that FDA should limit the "ability" to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than permitting non-physicians to apply to be certified prescribers, because of the regimen's serious risks and because physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age (Petition at 4). We do not agree.

Healthcare providers who are licensed to prescribe can become certified in REMS programs if they are able to meet the applicable REMS requirements. To become certified to prescribe mifepristone under the Mifepristone REMS Program, the prescriber must review the prescribing information for mifepristone and complete a Prescriber Agreement Form. By signing the form, the prescriber agrees that they meet certain qualifications, including the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also: (1) be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care; or (2) be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.[24]

In our review of the S-020 efficacy supplement in 2016, we determined that available data support that Mifeprex is safe and effective when prescribed by midlevel providers, such as physician assistants and nurse practitioners, as well as by physicians.[25] Our 2016 review included four studies that evaluated the safety and efficacy of medical abortion when performed by non-physician healthcare providers. Two trials evaluated the currently

[23] Petition at 4, fn. 6 (citing Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21).
[24] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf; see also https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[25] See 2016 Clinical Review, supra n. 13, at 79; see also 2016 Cross-Discipline Team Leader Review, supra n. 19, at 17-18. We also note that in most states, midlevel clinicians, such as physician assistants and nurse practitioners, are licensed to prescribe medications.

approved Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner);[26,27] one trial studied a regimen using vaginal misoprostol (Warringer);[28] a fourth study did not specify the route of misoprostol administered (Puri).[29] Olavarrieta reported a completion rate of 97.9 percent when medical abortion was provided by nurses as compared with 98.4 percent with physicians. Kopp Kallner reported a completion rate of 99 percent with certified nurse midwives versus 97.4 percent with physicians. Warriner reported an abortion completion rate of 97.4 percent with nurses as compared with 96.3 percent with physicians. Puri reported an abortion completion rate of 96.8 percent when the service was provided by nurse-midwives as compared with 97.4 percent in the "standard care" group.[30] Our 2016 review also included a systematic review of six controlled clinical studies by Renner;[31] the authors concluded that the evidence "indicates that trained mid-level providers may effectively and safely provide first trimester surgical and medical termination of pregnancy services." Additionally, Barnard et al., in a Cochrane systematic review, assessed the safety and effectiveness of abortion procedures administered by mid-level providers (nurse practitioners, midwives, other non-physician healthcare providers) compared to doctors.[32] The authors concluded, based in part on two of the studies that we had reviewed in 2016,[33] that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors.

We also believe that the identification of patients for whom the use of mifepristone is contraindicated can be done by mid-level healthcare providers, as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:[34]

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass

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[26] Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus Physician-provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial. Bull World Health Organ. 2015;93:249-258.

[27] Kopp Kallner H, Gomperts R, Salomonsson E, et al. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. BJOG. 2015; 122: 510-517.

[28] Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet. 2011; 377: 1155-61.

[29] Puri M, Tamang A, Shrestha P, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. Reproductive Health Matters. 2015; 22(44) 94-103.

[30] 2016 Clinical Review, supra n. 13, at 43.

[31] Renner RM, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. BJOG 2013 Jan;120(1):23-31.

[32] Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). Cochran Database of Systematic Reviews. 2015, Issue 7.

[33] Of the medical abortion studies reviewed by Barnard et al (Id.), two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al (supra n. 28) and Kopp Kallner et al (supra n. 27). The third used a different dose of misoprostol than the currently approved regimen. See Jejeebhoy SJ, Kalyanwalaa S, Zaviera AJF, Kumara R, Mundleb S, Tankc J, et al. Feasibility of expanding the medication abortion provider based in India to include avurvedic physicians and nurses. International Perspectives on Sexual and Reproductive Health 2012;38(3)133-42)

[34] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

- An intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandins
- Hemorrhagic disorder or concurrent anticoagulant therapy
- Inherited porphyrias

These contraindications can be assessed by trained healthcare providers who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. We continue to believe that available data support the conclusion that mid-level healthcare providers, as well as physicians, possess the clinical and counseling skills necessary to provide medical abortion. We note this is consistent with ACOG's statement in its current practice bulletin that "[i]n addition to physicians, advanced practice clinicians, such as nurse-midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion."[35] Further, if necessary, ultrasound training and certification is available to nurse practitioners and physician assistants, as well as physicians.[36] In sum, available information supports that mid-level healthcare providers as well as physicians can determine whether mifepristone is an appropriate treatment for a particular patient and dispense it.

You also assert that FDA should strengthen the requirement that providers accurately assess the duration of the pregnancy by mandating that gestational age be assessed by ultrasound (Petition at 5). We refer you to FDA's 2016 Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (the "2016 CP Response"), where FDA stated that the determination of gestational age does not always require an ultrasound. In the 2016 CP Response, FDA stated it had "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS [transvaginal ultrasound]) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider."[37]

In the Petition, you reference the Prescriber Agreement Form, in which the provider must attest they have the ability to: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed (or have made plans to provide such care through others), and you state that a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional

[35] ACOG Practice Bulletin No. 225, supra n. 22.
[36] American Institute of Ultrasound in Medicine. Accessed November 26, 2021. https://www.aium.org/officialStatements/70.
[37] FDA's citizen petition response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical and Dental Association, and Concerned Women for America on August 20, 2002, Docket No. FDA-2002-P-0364 at 18. See https://www.regulations.gov/document/FDA-2002-P-0364-0002.

contraindications (Petition at 5-6). You state that FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4).

Certified prescribers do not have to be physically present with the patient as long as they have confirmed the patient's gestational age and intrauterine pregnancy. As noted above, in the 2016 CP response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."[38] Moreover, the evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber and can be done in different types of healthcare settings. A certified prescriber can also review the Patient Agreement Form[39] with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity. See also section II.B.1.c (ETASU C – In-person Dispensing).

With respect to providing surgical intervention in cases of incomplete abortion or severe bleeding and assuring patient access to medical facilities equipped to provide blood transfusions and resuscitation (if necessary), the Prescriber Agreement Form does not reflect a requirement that the certified prescriber must provide such care personally; rather, the prescriber must agree that they have the ability to provide such care or that they have made plans to provide such care through others, and that they have the ability to assure the patient has access to appropriate medical facilities. It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients, and in many places, hospitals employ "hospitalists" to provide care to all hospitalized patients. We also note ACOG's statement that "[i]n rare cases, a patient who undergoes a medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral."[40]

For these reasons, we deny your request that FDA limit the "ability" to prescribe and dispense mifepristone to licensed physicians, and we deny your request that FDA require certified providers to physically meet with and examine the patient.

b. Office Visits and Administration of Mifepristone/Misoprostol

In the Petition, you state that the use of mifepristone and misoprostol should require three office visits by the patient (Petition at 7). In support of this position, you state the following:

- Drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10).

[38] Id.
[39] See https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[40] ACOG Practice Bulletin Number 225 supra n. 22.

- Abortion complications are more frequent when women abort at home and more healthcare oversight is needed (Petition at 8).

- Home administration of misoprostol does not permit healthcare providers to control when their patients take misoprostol and without monitoring:

    - a patient may take buccal misoprostol before the minimum 24-hour period after taking Mifeprex, which leads to a significantly increased failure rate (Petition at 7).

    - a patient may swallow misoprostol rather than administer it buccally, and oral administration is not as effective as buccal administration in ending the pregnancy (Petition at 7).

- Because providers may now "confirm" that a patient's drug-induced abortion was successful without a clinic visit, this increases the threat that Rh-negative patients will not receive Rhogam, which is necessary to prevent serious risks in subsequent pregnancies (Petition at 7 and 9).

We address each of these points below.

i. Follow-up Care

The safe use of mifepristone when used in the approved regimen with misoprostol is not contingent on a specific number of office visits being made by the patient undergoing a medical termination of pregnancy. The 2016 labeling change for Mifeprex regarding post-treatment assessment, including the change to the approved regimen to reduce the number of offices visits from three to one, was based on evidence reviewed in the S-020 efficacy supplement. We concluded, upon reviewing the data, that three office visits were not necessary to assure the safe use of Mifeprex.[41]

In your Petition, you point to statements by ACOG that medical abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 8, 10). The ACOG statements you point to are from ACOG Practice Bulletin No. 143, which has been withdrawn and replaced by Practice Bulletin No. 225.[42] Neither of the statements from the withdrawn Practice Bulletin nor Practice Bulletin No. 225 contraindicate medical abortion in women who are not available for an in-clinic follow-up visit. The current ACOG recommendations indicate that for medical abortion, "[f]ollow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[43] The patient and their healthcare provider should determine the best option for follow-up as part of the consultation and consent process.[44] As reflected in ACOG's guidance, appropriate follow-

[41] See 2016 Clinical Review, supra n. 13, at 44 and 64-67.
[42] ACOG Practice Bulletin Number 225, supra n. 22.
[43] Id.
[44] Id.

up after medical termination of a pregnancy may be accomplished in multiple ways and not all require an in-clinic visit.

You also question findings in multiple studies that evaluated the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, or MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies and assessed the ability of patients to self-administer these tests and interpret the test results (Petition at 9-10). Overall, these studies concluded that in the majority of women, it is feasible to use a simplified test to determine if further follow-up is necessary. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion completed at home versus routine clinic follow-up after medical abortion, concluding self-assessment was not inferior to routine clinic follow-up.[45] We note that this is consistent with current ACOG recommendations, which state that "follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[46]

You also assert that it is important for a patient to be under observation after taking misoprostol to ensure that they are appropriately monitored and provided sufficient pain medication (Petition at 8). You cite the World Health Organization (WHO)'s statement in guidance that up to 90 percent of women will abort within 4-6 hours after taking misoprostol; you further state that the 2000 regimen permitted patients to be in the clinic during this time period (Petition at 8). Your reference to the WHO guidance document[47] appears to be out of context. The WHO guidance takes no position on whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol; in fact, it explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.[48] In the United States, and as reflected in the approved labeling, medical termination of pregnancy usually involves patients terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

ii. At Home Medical Abortion and Healthcare Oversight

In addition, you cite a 2018 study to support your statement that abortion complications are more frequent when women abort at home (Petition at 8). The study evaluated complications following medical abortion (both less than 12 weeks and more than 12 weeks gestation) as well as following surgical abortion, at one hospital in Sweden between 2008 and 2015.[49] For the years 2008 to 2010, data were collected retrospectively; for the years

[45] Baiju, N, Acharya, G, D'Antonio, F, et al. 2019. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. BJOG; 126:1536-1544.
[46] ACOG Practice Bulletin Number 225, supra n. 22.
[47] World Health Organization, Safe Abortion: technical and policy guidance for health systems – 2nd edition. 2012. Page 45 and Section 2.2.2.1 Medication for pain.
[48] Id. at Section 2.3 Post-abortion care and follow-up, at 52.
[49] Carlsson I, Breding K, Larsson PG, 2018, Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study, BMC Women's Health 18:158.

2011 to 2015, data were collected prospectively. In this study, medical abortions after 12 gestational weeks all occurred at the hospital. The authors report that, among medical abortions less than 12 weeks, the complication frequency increased from 5.4 percent (2008 to 2010) to 8.2 percent (2015). However, the authors also compared the complications related to medical abortions that occurred at less than 12 gestational weeks between "at home" abortions (managed as an outpatient) and "at the hospital" abortions, in 2015 and found no statistically significant difference (8.2 percent "at home" versus 8.0 percent at the hospital). For pregnancies less than or equal to 9 gestational weeks, the rates are similar for the "at home" group (10.0 percent) and the "at the hospital" group (9.3 percent). Notably, as part of our review and approval of the S-020 efficacy supplement in 2016, we assessed serious adverse events by gestational age, including hospitalizations, serious infection requiring hospitalization or intravenous antibiotics, bleeding requiring transfusion, and ectopic pregnancy, as reported in the literature submitted by the Applicant. We concluded that these serious adverse events are rarely reported in the literature and that the regimen of mifepristone 200 mg followed by buccal misoprostol 800 mcg in 24-48 hours is safe to approve for use through 70 days gestation.[50]

You also state that medical abortion is a longer process than surgical abortion and that it requires more attention and care from healthcare providers (Petition at 10). We agree that medical abortion can be a longer process than surgical abortion,[51] but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. Not all of the complications associated with medical abortion necessarily require more intensive management from healthcare providers during a follow-up visit. The question of whether to include an in-person follow-up visit should be discussed by the healthcare provider and the patient. We have concluded that medical abortions are safe and effective for patients who are appropriate candidates and reducing the number of clinic visits does not compromise patient safety.

The current approved labeling for mifepristone for medical termination of pregnancy states that complete pregnancy termination "can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan." Not all these modalities require an in-clinic assessment during a follow-up visit. Our review of the S-020 efficacy supplement concluded that "available data support … that there are a variety of follow-up modalities that can adequately identify the need for additional intervention."[52] We note that these findings are also consistent with ACOG guidelines, which state that "[r]outine in-person follow-up is not necessary after uncomplicated medication abortion" and recommend several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at one week after treatment followed by urine pregnancy testing at four weeks after treatment.[53] Because there is more than one effective method to detect an on-going pregnancy, we conclude that the way in which post-treatment follow-up is performed may be determined by the healthcare provider and the patient.

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[50] 2016 Clinical Review, supra n. 13, at 51-57.
[51] See ACOG Practice Bulletin Number 225, supra note 22.
[52] 2016 Cross Discipline Team Leader Review, supra n. 19, at 17.
[53] ACOG Practice Bulletin Number 225, supra note 22.

iii. Misoprostol

In the Petition, you make a number of assertions regarding the use of misoprostol. We address each in turn.

First, you assert that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex, thereby rendering the regimen ineffective, and that home administration of misoprostol does not permit health providers to control when their patients take misoprostol (Petition at 7). You similarly assert that the use of buccal misoprostol sooner than 24 hours after administering mifepristone leads to significantly increased failure rates (Petition at 7).

As an initial matter, our review of the S-020 efficacy supplement in 2016 included data that evaluated the home use of misoprostol in over 30,000 women. The data showed that Mifeprex was safe and effective in a regimen with misoprostol when misoprostol was self-administered at home.[54] Therefore, any incorrect administration resulting in a failed abortion was infrequent and did not significantly affect the safety and efficacy of medical abortion. Furthermore, because the process of expelling the pregnancy may begin as soon as 2 hours after taking misoprostol, there is a benefit in allowing patients to choose when and where to start this process, to maximize the possibility of their being at a safe place at a convenient time to experience cramping and bleeding.[55]

In support of your assertion of significantly increased failure rates, you cite a pilot study by Lohr et al.[56] Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (less than or equal to 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations[57] using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates reported by Lohr at 24 hours for oral mifepristone and buccal misoprostol were 72.5 percent, 69.2 percent, and 72.5 percent, respectively; the complete abortion rates at two weeks, however, were 97.5 percent, 100 percent, and 94.9 percent, respectively (and are consistent with the completion rates as described in the approved labeling).[58] The published complete abortion rates at 24 hours for simultaneous oral mifepristone and vaginal misoprostol administration were 90 percent, 88 percent, and 83 percent, respectively, for the gestational age groupings and the complete abortion rates at 2 weeks were 98 percent, 93 percent, 90 percent, respectively. Based on the data presented in Lohr,

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[54] See 2016 Clinical Review, supra n. 13, at 41 and 48.
[55] Id. at 38.
[56] Petition at 7 (referencing Lohr PA, Reeves MF, Hayes JL, et al., 2007, Oral Mifepristone and Buccal Misoprostol Administered Simultaneously for Abortion: A Pilot Study, Contraception, 76:215-220).
[57] Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. Contraception 2005;71:447–50; Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. Contraception 2005;71:333–6.
[58] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. As recommended in Section 2.3 of the approved labeling, follow-up at 7-14 days after administration of mifepristone is more appropriate to evaluate efficacy.[59] It is misleading to only reference the abortion completion rates observed at the 24-hour timepoint from Lohr. Therefore, we do not agree that data from Lohr indicate higher failure rate with misoprostol taken before the prescribed minimum 24-hour period after taking mifepristone.

Although we disagree that Lohr demonstrates a higher failure rate with misoprostol taken before 24-hours after taking mifepristone, we note that our 2016 review of the S-020 efficacy supplement referenced a 2013 systematic review by Raymond, which concluded that if the interval between mifepristone and misoprostol interval is less than or equal to 24 hours, the procedure is less effective compared to an interval of 24-48 hours.[60] As explained above, the data reviewed in 2016 showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective. Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. However, in light of the data reviewed, section 2.1 of the labeling approved in 2016 (as well as the currently approved labeling and Medication Guide) states that there should be a "minimum 24-hour interval between" mifepristone and misoprostol (emphasis included in the labeling).[61] The approved dosing regimen also states that misoprostol is taken within 24 to 48 hours after taking mifepristone and acknowledges that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration.

In addition to your concerns that a woman may take misoprostol too soon after administering mifepristone, you also state that waiting until 24 hours after administering mifepristone does not guarantee success (Petition at 7-8). In support of this concern, you cite a 2015 review by Chen and Creinin. You state that this review found "women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen" (Petition at 8). Chen and Creinin included studies in which the intervals between mifepristone and buccal misoprostol were 24 hours or 24-48 hours and stated that "based on the available literature, the overall efficacy of regimens with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2 percent compared with 96.8 percent)."[62] The rate differences were statistically significant, but both regimens were more effective than the 92 percent efficacy rate of the original regimen approved in 2000 (administering misoprostol 48 hours after taking mifepristone).

Finally, you also express concern that if misoprostol is self-administered, a woman may swallow it rather than keep the pill between her cheek and gum, and oral administration of

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[59] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.
[60] 2016 Clinical Review, supra n. 13, at 31 (citing 8 Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.)
[61] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.
[62] See Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. Obstet Gynecol. 2015;126(1):12-21; see also 2016 Clinical Review, supra n. 13, at 21.

misoprostol (i.e., swallowing the pill) following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy (Petition at 7). Winikoff et al. specifically studied the use of oral compared to buccal misoprostol 24-36 hours after mifepristone 200 mg with overall success rates of 91.3 percent and 96.2 percent, respectively.[63] Both regimens resulted in a greater than 91 percent successful medical abortion. Although the study showed decreased efficacy with oral versus buccal administration in 57-63 days gestational age, there were no statistical differences in other gestational age groupings. Even assuming there is a small proportion of women who are 57-63 days gestational age and use oral administration of misoprostol (rather than buccal as labeled), a small decrease in the reported efficacy in that population would not justify requiring a clinic visit for all women undergoing medical abortion.

Overall, studies support the efficacy of the mifepristone, in a regimen with misoprostol when taken by the patient at home, Therefore, we do not agree that an in-person visit is necessary to manage administration of misoprostol.

iii. Rh-Negative Patients

In the Petition, you state that a follow-up examination is particularly critical for Rh-negative patients and that without that follow-up examination, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9). You suggest that a clinic visit after the administration of Mifeprex is important for Rh-negative women to receive Rhogam and that removing the required follow-up visit puts Rh-negative women at risk for isoimmunization. We do not agree.

Rh testing is standard of care in the United States and RhD immunoglobulin (such as Rhogam) should be administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).[64] However, the facility where the RhD immunoglobulin injection occurs (clinic, hospital or laboratory) is not critical. A shift from medical clinics to hospitals for administration of injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.[65] This has resulted in pregnant women frequently obtaining routine 28-week RhD immunoglobulin injections at hospitals/laboratories with a prescription provided by their healthcare providers. This same process of obtaining RhD immunoglobulin via prescription is available to patients after medical termination of pregnancy and does not require a follow-up clinic visit.

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[63] Winikoff B, Dzuba, IG, Creinin MD, et al, 2008, Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion, Obstet Gynecol 112(6):1303-1310.

[64] ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.

[65] See https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers.

In summary, the totality of data on the efficacy and safety of medical abortion at less than 70 days gestation, derived from numerous studies, has characterized the complications and rates of complications for completing medical abortion at home, and the findings show medical abortion at home is both safe and effective without three office visits. We therefore deny your request that the use of mifepristone in a regimen with misoprostol require three office visits by the patient.

c. Contraindications

In the Petition, you assert that critical language contraindicating Mifeprex for patients without access to appropriate emergency medical care was excluded from the 2016 Mifeprex labeling. You cite to a study[66] and ACOG statements as evidence that medical abortions have greater risks and more need for emergency "operation" than a surgical abortion, particularly for patients in rural areas with limited access to emergency medical care (Petition at 11).

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in section 4 of the approved labeling when we approved the S-020 efficacy supplement, the 2016 Mifeprex labeling and the currently approved mifepristone labeling, as well as the Mifepristone REMS Program, continue to include appropriate instructions for providers regarding patient access to appropriate medical care.[67] For example, the Boxed Warning includes language directing healthcare providers to ensure that the patient knows whom to call and what to do, including potentially going to an emergency room, if the patient experiences serious events associated with the use of mifepristone. The labeling also directs healthcare providers, as part of the dosing regimen, to give the patient the name and phone number of a healthcare provider who will be handling emergencies.[68] In addition, one of the required qualifications listed in the Prescriber Agreement Form is the "[a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."[69] Therefore, although certain language about access to medical facilities was removed from the approved labeling in 2016, we disagree that critical language about access to appropriate emergency medical care is lacking from the approved labeling.

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[66] See Petition Reference Document No. 17 (Harrison Affidavit: Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015), ¶115 (referencing M. Niinimaki et al., Immediate Complications after Medical compared with Surgical Termination of Pregnancy, Obstet. Gynecol. 114:795 (Oct. 2009)).

[67] See Mifeprex labeling, approved 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf. See also current labeling at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

[68] Id.

[69] Mifepristone REMS Program, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390. Emphasis added.

You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.[70] As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

d. Adverse Event Reporting

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

[70] Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.

You state that FDA should provide guidance to emergency healthcare providers and physicians so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13). We disagree that specific guidance is needed at this time. In the past, when appropriate, FDA has worked with the NDA Applicant to issue communications to healthcare providers and emergency department providers concerning certain serious adverse events.[71] Furthermore, the approved Medication Guide advises patients to take the Medication Guide with them if they need to go to the emergency room or seek care from a healthcare provider other than the one who dispensed the medication to them, so the emergency room or healthcare provider understands the patient is having a medical abortion. We have not identified a change in the safety profile of mifepristone that would warrant additional communications to healthcare providers and emergency department providers concerning complications following medical abortion. If we become aware of safety information that merits further communications with emergency department providers or healthcare providers, or that warrants revisions to the approved labeling, we will act as appropriate.

You also assert that many Mifeprex prescribers "violate FDA protocol," instructing their patients to lie to emergency medical personnel, and that this prevents emergency healthcare providers from appropriately caring for their patients and further decreases the likelihood that adverse events will be reported (Petition at 12). Your only support for this claim is a reference to instructions from the organization Aid Access[72] to patients that they can tell emergency room staff that they had a miscarriage and do not need to tell medical staff that they had a medical abortion. The Petition does not provide any data or additional information establishing "many Mifeprex prescribers violate FDA protocol, instructing their patients to lie," or that these providers thereby prevented appropriate care and decreased the number of adverse events reported.

B. REMS

1. Request to Retain Mifeprex REMS

In your Petition, you request that FDA retain the Mifeprex REMS (Petition at 14). We agree that a REMS is necessary to ensure that the benefits of mifepristone in a regimen with misoprostol outweigh the risks. FDA's determination as to whether a REMS is necessary

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[71] See Historical Information on Mifepristone (Marketed as Mifeprex), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm. For example, the NDA applicant and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 and a Dear Emergency Room Director letter in September 2004. The fact that these letters were issued does not imply that the approved mifepristone regimen is unsafe; it is not uncommon for drug sponsors to issue "Dear Health Care Provider" letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, "[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely."

[72] We note that Aid Access facilitated the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA sent Aid Access a warning letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers. US FDA Warning Letter to Aidaccess.org, dated March 8, 2019. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019.

to ensure that the benefits of a drug outweigh its risks is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case.[73] In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.[74]

As described in the background section of this response (see section I.A.), FDA determined that interventions in addition to the FDA-approved labeling were necessary to ensure that the benefits of Mifeprex outweighed its risks when the drug was initially approved in 2000, and periodic re-evaluations of the REMS since that time have reached the same conclusion. As further described in the background section of this response (see section I.E.), FDA recently undertook a review of the Mifepristone REMS Program. As explained below, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risks.

After review of multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FAERS reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation,[75] as well as information submitted by the Applicants, we have concluded that the REMS can be modified to reduce the burden on the health care delivery system without compromising patient safety. As explained below, we agree that the healthcare provider certification (ETASU A) and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions (ETASU D) continue to be necessary components of the REMS to ensure the benefits outweigh the risks. However, we have concluded that the Mifepristone REMS Program must be modified to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

Below, we discuss each of these elements of the Mifepristone REMS Program.

a. ETASU A – Prescriber Certification/Qualifications

ETASU A under the Mifepristone REMS Program requires healthcare providers who prescribe mifepristone to be certified. In order to become certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the Prescriber Agreement Form. In signing the Prescriber Agreement Form, prescribers agree they meet the qualifications listed below:

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[73] See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Apr. 2019).
[74] Id.
[75] See supra n. 10.

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the Patient Agreement Form with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

Our review of the published literature did not identify any studies comparing healthcare providers who met these qualifications with healthcare providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention either personally or through others, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our conclusion continues to be that a healthcare provider who prescribes mifepristone in a regimen with misoprostol should meet the above qualifications. Absent these provider qualifications, we are concerned that serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, may not be detected or appropriately managed.

Accordingly, we have determined that ETASU A must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks. Maintaining the requirement for prescriber certification ensures that providers meet the necessary qualifications and adhere to the guidelines for use listed above. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one-time for each applicant.

Although we agree with your request to retain the REMS for mifepristone (now the Mifepristone REMS Program) insofar as it pertains to ETASU A, as discussed in section II.A.2.a of this response, we do not agree with your request that the healthcare provider needs to be a licensed physician to meet this requirement.

b. ETASU D – Requirement For The Drug To Be Dispensed With Evidence Or Other Documentation Of Safe-Use Conditions

ETASU D under the Mifepristone REMS Program requires mifepristone to be dispensed with evidence or other documentation of safe-use conditions. To receive mifepristone for medical termination of intrauterine pregnancy through 70 days gestation, the patient must sign a Patient Agreement Form indicating that the patient has received, read, and been provided a copy of the Patient Agreement Form and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The Patient Agreement Form ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication. In a number of approved REMS, Patient Agreement Forms or Patient Enrollment Forms ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[76]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the Patient Agreement Form with the patient, fully explaining the risks of the treatment regimen and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the Patient Agreement Form, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the Patient Agreement Form serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed Patient Agreement Form in the patient's medical record.

In addition, we conducted an updated review of published literature since 2016 to assess the utility of maintaining the Patient Agreement Form as part of the Mifepristone REMS Program, and these studies do not provide evidence that would support removing ETASU D. For these reasons, we have determined that ETASU D must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks.

[76] REMS@FDA, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.

c. ETASU C – In-Person Dispensing

ETASU C under the Mifepristone REMS Program currently requires mifepristone to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. This creates what we refer to in this response as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office, or hospital when the drug is dispensed. The mifepristone REMS document currently states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than a clinic, medical office, or hospital. As explained below, based on a recent review of the REMS, we believe that the Mifepristone REMS Program must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks. This conclusion is based on our review of information from the Mifepristone REMS Program one-year (1st) REMS[77] assessment data and postmarketing safety information, and supported by our review of the published literature.

i. Assessment Data

As part of our review of the REMS, we evaluated information included in the 1st REMS assessment report for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, and non-compliance data. This 1st REMS assessment report covers a reporting period between April 11, 2019 through February 29, 2020. During this reporting period, a small number of non-compliance events were reported.

As described in section I.C. of this response, during the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not enforced. To better understand whether there was any impact on safety or non-compliance during the periods when the in-person dispensing requirement was not enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or non-compliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. The NDA and the ANDA Applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no

[77] This REMS assessment report was the first submitted following the approval of the single, shared system REMS for mifepristone.

indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events.

ii. FAERS/Postmarketing Safety Data

FDA routinely monitors postmarketing safety data for approved drugs through adverse events reported to our FAERS database,[78] through our review of published medical literature, and when appropriate, by requesting applicants submit summarized postmarketing data. For our recent review of the REMS, we searched our FAERS database, reviewed the published medical literature for postmarketing adverse event reports for mifepristone for medical termination of pregnancy, and requested that the Applicants submit a summary and analysis of certain adverse events. Our review of this postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced.

In order to evaluate the periods when in-person dispensing was and was not enforced, we conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy. The data for this time period were then further divided into the date ranges when in-person dispensing was enforced per the REMS (January 27, 2020 - July 12, 2020 and January 13, 2021 - April 12, 2021) versus when in-person dispensing was not enforced: July 13, 2020 - January 12, 2021 (in-person dispensing enforcement was temporarily enjoined) and April 13, 2021 - September 30, 2021 (enforcement discretion for in-person dispensing because of the COVID-19 PHE).

Based on the above search, a total of eight cases were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when in-person dispensing was being enforced (i.e., January 27, 2020-July 12, 2020 and January 13, 2021-April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when in-person dispensing was not enforced (i.e., July 13, 2020-January 12, 2021 and April 13, 2021-September 30, 2021); however, the narratives provided in the FAERS reports for three of the five cases explicitly stated that mifepristone was dispensed in-person. These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Of note, ongoing pregnancy and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case reported the occurrence of oral pain/soreness (case 8) in July

[78] FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

2021, but did not provide sufficient information to determine the exact date of the adverse event.

As discussed in section II.A.2.d., the Applicants report adverse events, including serious adverse events, to FDA in accordance with applicable regulations.[79] To enable additional review of adverse events, Applicants were requested to provide a summary and analysis for adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided the requested summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021. The Applicant for the generic provided the requested summary of postmarketing safety information from April 11, 2019 (date of initial approval) through September 30, 2021. The information provided by the Applicants included the same cases identified in FAERS, as discussed above.

We analyzed the FAERS data referenced above to determine if there was a difference in adverse events when in-person dispensing was and was not enforced. Based on FDA's review of this data, we concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced and that mifepristone may be safely used without in-person dispensing. FDA's review of the summary and analysis data submitted by the Applicants (which, as noted above, included the same cases identified from FAERS) did not change this conclusion.

iii. Published Literature

As noted above, we also conducted an extensive review of the published literature since March 29, 2016 (the date the S-020 efficacy supplement for Mifeprex was approved) through September 30, 2021.[80] Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or equivalent healthcare provider in countries other than the United States). Some studies have examined replacing in-person dispensing in certain healthcare settings with dispensing at retail pharmacies[81]

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[79] See 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81.

[80] In support of your request that we retain the REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber, you reference two studies that you assert do not comply with the REMS (Petition at 19-22). Outcomes from both of the studies you reference have been reported in the published literature and are addressed in the discussion that follows. We note that as a general matter, a clinical investigation of an approved drug that is subject to a REMS can take place in healthcare settings outside those provided for in the REMS. When an approved drug that is subject to a REMS is studied in a clinical trial, the REMS does not apply to the use of the drug in that clinical trial. However, FDA reviews the protocol to ensure that it will be conducted in a manner that adequately addresses the risks that the REMS is intended to mitigate, such that the trial participants will not be exposed to an unreasonable and significant risk of illness or injury. See 21 CFR 312.42(b)(1)(i) and (b)(2)(i).

[81] Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. Obstet Gynecol 2021;137:613–22; Rocca CH, Puri M, et al. Effectiveness and safety of early medication

and dispensing mifepristone from pharmacies by mail.[82] Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to patients,[83] and (2) prescribers using couriered delivery of medications.[84] Different studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization."[85]

We note that the ability to generalize the results of these studies to the United States population is hampered by differences between the studies with regard to pre-abortion care (e.g., telemedicine versus in-person). In addition, the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy. There are also factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation (for example, most studies on mail dispensing of mifepristone also include telemedicine consultation); and (2) because most serious adverse events with medical abortion are infrequent, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States. Despite the limitations of the studies we reviewed, we have concluded that overall the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

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abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. PLoS ONE 13(1): e0191174. https://doi.org/10.1371/journal.pone.019117; Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. Contracept X. 2020; 2: 100023.

[82] Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2021, ISSN 0010-7824, https://doi.org/10.1016/j.contraception.2021.09.008, Available online 20 September 2021; Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. JAMA Network Open. 2021;4(8):e2122320, doi:10.1001/jamanetworkopen.2021.22320; Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. Aust N Z J Obstet Gynaecol 2018;58: 335-340.

[83] See Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. Contraception 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online. Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. Contraception 2019; 100:173-177. See also Chong et al., infra n. 103 Kerestes et al., infra n. 105, and Aiken et al., infra n. 106.

[84] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.

[85] Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. BJOG 2019;126;609-618. Norten H, Ilozumba O, Wilkinson J, Gemzell Danielsson K, Gomperts R. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. BJOG 2021; https://doi.org/10.1111/1471-0528.16765; Aiken ARA, Digol I, Trussell J, Gomperts R. Self-reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. BMJ 2017;357:j2011 http://dx.doi.org/10.1136/bmj.j2011.

Below is a summary of our review of the literature, organized by the methods of dispensing mifepristone that were studied.

(a) Retail pharmacy dispensing

Three studies reported medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation (Grossman,[86] Rocca,[87] Wiebe[88]). Grossman conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic. Complete abortion without additional procedures occurred in 93.5 percent of participants with known outcomes. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. No participants experienced a serious adverse event, were hospitalized or required transfusion. Three participants had emergency department (ED) visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study safety and efficacy outcomes are consistent with labeled outcome frequencies. The study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to United States retail pharmacies; there is insufficient information to assess this.

Rocca[89] conducted an observational study evaluating participants who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. The authors reported that, with respect to complete abortion (greater than 97 percent) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[90] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of women who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (equal to or greater than 95 percent participants with known outcomes). The telemedicine group had one case of hemorrhage (0.5 percent) and one case of infection requiring antibiotics (0.5 percent) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3 percent compared to 1.5 percent in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

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[86] Grossman et al., supra n. 81.
[87] Rocca et al., supra n. 81.
[88] Wiebe et al., supra n. 81.
[89] Rocca et al., supra n. 81.
[90] Wiebe et al., supra n. 81.

None of the three studies allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the results of the studies to the current retail pharmacy environment in the United States. The outcome findings from the one United States study (Grossman)[91], in which the pharmacies were partnered with prescribers, are unlikely to be broadly generalizable to the current retail pharmacy environment and do not reflect typical prescription medication availability with use of retail pharmacy dispensing. For the retail pharmacy dispensing study in Canada (Wiebe),[92] timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that would allow timely access to medications for medical abortion would occur in retail pharmacies throughout the United States, suggesting the findings from that study may not be broadly generalizable. The third study (Rocca)[93] evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the United States retail setting.

(b) Mail order pharmacy

Three studies evaluated mail order pharmacy dispensing (Grossman,[94] Upadhyay,[95] Hyland[96]). Grossman published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. Complete abortion without additional procedures occurred in 96.9 percent of participants with known outcomes. Two (0.9 percent) participants experienced serious adverse events; one received a blood transfusion and one was hospitalized overnight. Nine (4 percent) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies.

Upadhyay[97] reports findings from a retrospective cohort study of women undergoing medical abortion in the United States without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Abortion outcome was determined by either an assessment on day 3 or a 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95 percent for participants with known outcomes and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. As recommended in Section 2.3 of the approved labeling, follow-up at

[91] Grossman et al., supra n. 81.
[92] Wiebe et al., supra n. 81.
[93] Rocca et al., supra n. 81.
[94] Grossman et al, supra n. 82.
[95] Upadhyay et al., supra n. 82.
[96] Hyland et al., supra n. 82.
[97] Upadhyay et al., supra n. 82.

7-14 days after administration of mifepristone is more appropriate to evaluate safety and efficacy. This study used a model with numerous deviations from standard provision of medical abortion in the United States, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[98] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. Complete abortions without additional procedures occurred in 96 percent of participants with documented outcomes and is consistent with labeled efficacy. Of the participants included in the analysis, 95 percent had no face-to-face clinical encounters after medications were mailed while 3 percent were admitted to the hospital and 2 percent had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up." The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. However, the reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported frequency of hospitalizations (3 percent) is higher than the less than 1 percent in the FDA-approved mifepristone labeling, conclusions on the safety findings cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that efficacy of medical abortion is maintained with mail order pharmacy dispensing. With respect to safety, in the Grossman study[99] the interim analysis, although small, does not raise serious safety concerns. Safety findings from the Hyland[100] study are difficult to interpret. Although only one transfusion is reported and the authors state the findings demonstrate safety, a higher hospitalization rate and lack of information on the reasons for hospitalization preclude reaching any conclusions about the safety findings. Lastly, the Upadhyay[101] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the United States.

(c) Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail. Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population exclusively: Raymond (outcomes from May 2016 to December

[98] Hyland et al., supra n. 82.
[99] Grossman et al., supra n. 82.
[100] Upadhyay et al., supra n. 82.
[101] Hyland et al., supra n. 82.

2018),[102] Chong (outcomes from May 2016 to September 2020)[103] and Anger (outcomes from March 2020 to September 2020).[104] A fourth study, Kerestes,[105] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020 and a fifth study, Aiken (2021)[106] reports outcomes of medical abortion up to 70 days gestational age in the United Kingdom before and during the COVID-19 PHE in a retrospective cohort study.

In Raymond,[107] complete abortion without additional procedures occurred in 93 percent of participants with known outcomes. There were two hospitalizations (one participant received a transfusion for severe anemia despite having had a complete abortion) and 7 percent of participants had clinical encounters in ED/urgent care centers. The reported outcomes are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).[108] Of note, the authors state that half of the ED/urgent care visits did not entail any medical treatment. In Chong,[109] approximately 50 percent of the medical abortions occurred during the period of the COVID-19 PHE. Complete abortion without an additional procedure occurred in 95 percent of those with known outcomes. Transfusions were 0.4 percent and hospitalizations were 0.7 percent; 6 percent of participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 4.1 percent to complete abortion. The reported outcomes in Chong (which updated the findings described in Raymond) are similar to outcomes described in approved labeling except that (as with the Raymond study it updated) the combined ED/urgent care center encounters (6 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).

Anger,[110] which compared outcomes among participants enrolled in the Gynuity study who did ("test medical abortion cohort") versus did not ("no-test medical abortion cohort")[111]

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[102] Raymond et al., supra n. 83.

[103] Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. Contraception 2021;104:43-48.

[104] Anger et al., supra n. 83.

[105] Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021 Jul;104(1):49-53. doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.

[106] Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. BJOG 2021;128:1464–1474.

[107] Raymond, supra n. 83.

[108] The authors reported the combined frequency of emergency department/urgent care visits, whereas the approved labeling includes the frequency for emergency department (emergency room) visits. Therefore it is unknown whether the frequency of emergency department visits in the trial, as distinct from the combined frequency of emergency department/urgent care visits, is comparable to the frequency of emergency department visits reflected in approved labeling.

[109] Chong et al., supra n. 103.

[110] Anger et al., supra n. 83.

[111] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al." (Raymond EG, Grossman D, Mark A, et.al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. Contraception 2020;101:361-366)

have confirmation of gestational age/intrauterine location with an examination or ultrasound, found that those without an examination or ultrasound prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.[112] There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the "test" group, complete medical abortion was confirmed in 98 percent of participants with known outcomes; one participant was "hospitalized and/or blood transfusion" and 8 percent had an unplanned clinic encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion). In the "no-test" group, complete medical abortion was confirmed in 94 percent of participants with known outcomes; two participants were "hospitalized and/or blood transfusion" and 12.5 percent had an unplanned clinical encounter.

Kerestes[113] included three different delivery models: traditional in-person visits, telemedicine consultation with in-person pick-up of medications, and telemedicine consultation with delivery of medications by mail (most of the latter were enrolled through Gynuity's TelAbortion study). Among participants with follow-up data, the rates of successful medical abortion without surgery were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine plus in-person pickup group). Although ED visits occurred the most frequently in the telemedicine plus mail group (four participants or 5.8 percent) and the least in the in-person group (two participants or 2.1 percent), the study reported no increases in other serious adverse events. Aiken (2021)[114] reported outcomes before and during the pandemic in a retrospective cohort study in the United Kingdom. The study compared the two cohorts: one before the pandemic with in-person visits and dispensing (traditional model) and one during the pandemic with either an in-person visit and in-person dispensing or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Complete abortion occurred in greater than 98 percent in both cohorts; the rate was slightly higher in the telemedicine group than in the in-person group. There were no significant differences in the rates of reported serious adverse events. The investigators' analysis determined that the efficacy and safety were comparable between both cohorts and concluded the hybrid model for medical abortion is effective and safe.

Taken together, data from the three Gynuity study reports (Raymond, Chong, and Anger), Kerestes, and Aiken (2021) support that efficacy of medical abortion was maintained when mifepristone was dispensed by mail from the clinic. Study reports of Raymond, Chong, and Kerestes all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail from the clinic, but without increases in other serious adverse events. Anger's comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. The Aiken (2021) study appears to be of sufficient

[112] We note that the two cohorts were not randomized in the Anger study; they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.
[113] Kerestes et al., supra n. 105.
[114] Aiken et al., supra n. 106.

sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, significant limitations include that the analysis was based on deidentified information and the investigators were unable to verify the outcomes extracted. Further, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

Notwithstanding the limitations discussed above, these studies overall support that dispensing by mail from the clinic is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use.

(d) Clinic dispensing by courier

Reynolds-Wright[115] reported findings from a prospective cohort study of participants at less than 12 weeks gestational age in Scotland undergoing medical abortion at home that provided mifepristone for pick up at the service or by couriered delivery to woman's home. The outcomes from this study in Scotland are consistent with the outcomes in the approved mifepristone labeling. However, the number of couriered deliveries was not reported. Thus this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. The study shares the same limitations as the Aiken (2021) study; the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

(e) Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail. WoW uses a model with numerous deviations from the standard provision of medical abortion in the United States. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Three studies (Endler, Norten, and Aiken (2017))[116] reported outcomes based on dispensing through this model. Endler and Norten reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail because neither provide meaningful outcomes data for consideration. Although Aiken (2017) is a large cohort study, the outcomes are self-reported and an unusually high rate of outcomes are unaccounted for; these limitations result in the data being insufficient to determine the safety of dispensing mifepristone by mail though a partner organization.

In sum, there are insufficient data from the literature we have reviewed to determine the safety and efficacy of dispensing from a retail pharmacy, by courier, or by a partner organization. With respect to dispensing mifepristone by mail, our review of the literature indicates that dispensing mifepristone by mail from the clinic or from a mail order

[115] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.
[116] Endler et al., Norten et al., and Aiken et al., supra n. 85.

pharmacy does not appear to jeopardize the efficacy of mifepristone for medical abortion. While the studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, the safety and efficacy outcomes reported in these studies remain within the ranges labeled for the approved mifepristone products. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other significant adverse events related to mifepristone use.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, and our review of the literature, we conclude that mifepristone will remain safe and effective if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added. Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the Mifepristone REMS Program, the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

In your Petition, you state that "[e]liminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls" and that "health care providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs" (Petition at 18-19).

We do not agree that eliminating the REMS requirement for the dispensing of Mifeprex in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of healthcare providers to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. There are many factors that contribute to patient safety, including evaluation of a patient, informed consent, development of a follow-up plan, and provision of a contact for emergency care. All of these can occur in many types of healthcare settings. The evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber.

You also assert that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19). We do not agree. Healthcare providers who prescribe mifepristone are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the American Medical Association that a healthcare provider-patient relationship is entered when the "physician serves a patient's medical needs;"[117] in the context of medical abortion, this

[117] See www.ama-assn.org/delivering-care/ethics/patient-physician-relationships.

healthcare provider-patient relationship continues until resolution of the pregnancy or transfer of care to another healthcare provider.[118]

We also note that patients who are not pregnant at the time of evaluation would not be appropriate candidates for being prescribed mifepristone for medical termination of pregnancy because they do not fulfill the approved indication of having an intrauterine pregnancy of up to 70 days gestation.

2. Other Safety Issues and Additional Studies

In support of your request that we retain the Mifeprex REMS, you cite the Council for International Organizations of Medical Sciences' (CIOMS) definition of "rare" to assert that because "about 1 out of 100 women" using Mifeprex and misoprostol require surgery, serious complications are common, not rare (Petition at 15-16).[119] Although we agree that certain elements of the Mifepristone REMS Program are necessary to assure the safe use of mifepristone, we do not agree with your assertion.

In the Petition, you state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and you cite the Medication Guide as stating "'*rarely*, serious and potentially life-threatening bleeding, infections, and other problems can occur following . . . medical abortion.' Specifically, 'in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure." (Petition at 15). Using these two separate statements in the Medication Guide, you argue that the CIOMS's definition of rare ("1 out of 1000") means that if 1 out of 100 women using Mifeprex in a regimen with misoprostol require surgery, serious complications are common, not rare. (Petition at 16). However, your reference to the two sentences in the Medication Guide conflates two different clinical scenarios: (1) the adverse event of serious and potentially life-threatening bleeding, and (2) treatment failure.

The first sentence you reference states: "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." This statement refers to life-threatening adverse events that can occur during termination regardless of gestational age or during miscarriage or childbirth regardless of the mode of delivery (e.g., vaginal delivery or cesarean section). At the time of our review of the clinical studies submitted to support the S-020 efficacy supplement, the reported rate of death in the studies reviewed, based on one death, was 0.007 percent (very rare under the CIOMS definition).[120] The rate of infections requiring hospitalization or

[118] See https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine.
[119] Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition. 1999. https://cioms.ch/wp-content/uploads/2018/03/Guidelines-for-Preparing-Core-Clinical-Safety-Info-Drugs-Report-of-CIOMS-Working-Group-III-and-V.pdf. Accessed December 13, 2021 (CIOMS).
[120] Id. at 36 (defining the "very rare" standard category of frequency as less than 0.01 percent).

intravenous antibiotics was less than 0.1 percent (rare under the CIOMS definition),[121] and rates of transfusion were 0.03-0.7 percent (rare to uncommon under the CIOMS definition).[122] Therefore, "rarely" accurately refers to the frequency of the adverse events referenced in this statement.

The second sentence you reference from the Medication Guide states: "In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C)." This statement refers to the rate of surgical procedures for bleeding following treatment with mifepristone. Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the CIOMS definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion. Furthermore, in the vast majority of medical abortions, surgical intervention is not necessary.

You also cite a 2009 study and a 2018 study to assert that medical abortions carry greater risks than surgical abortions (Petition at 16). The 2009 Niinimaki, et al.[123] study reported overall incidences of immediate adverse events (up to 42 days) in medical and surgical abortions performed in women undergoing induced abortion from 2000-2006 based on data from the Finnish national registries. We agree that the overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0 percent versus 5.6 percent). Specifically, the incidence of hemorrhage, incomplete abortion, and surgical (re)evacuation were higher for medical abortion. However, the authors specifically noted that because medical abortion is associated with longer uterine bleeding, the high rate of events, which were pulled from a national registry reflecting both inpatient and outpatient visits, is not surprising. They opined that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy; the incidence of such bleeding was relatively low, although it was more common with medical abortion. In addition, the authors acknowledged there are inherent weaknesses in registry-based studies; there is variable reliability both of diagnoses and of severity of diagnoses. Nevertheless, the authors concluded that both methods are generally safe and recommended discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination.

We note that Ireland, et al.[124] reported findings from a more recent retrospective cohort study of 30,146 United States women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6 percent and 99.8 percent for medical and surgical abortion, respectively.

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[121] Id. at 36 (defining the "rare" standard category of frequency as greater than or equal to 0.01 percent and less than 0.1 percent).
[122] Id. at 36 (defining the "uncommon" standard category of frequency as greater than or equal to 0.1 percent and less than 1 percent); see also 2016 Clinical Review, supra n. 13, at 47 and 51.
[123] Niinimaki M, Pouta A, Bloigu A, et al. Immediate complications after medical compared with surgical termination of pregnancy. Obstet Gynecol. 2009;114(4):795-804.
[124] Ireland LD, Gatter, M, Chen, A. 2015. Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the Frist Trimester. Obstetrics & Gynecology 126;22-28.

Unanticipated aspiration for persistent pain, bleeding or both were 1.8 percent and 0.4 percent for medical and surgical abortion respectively. These findings are compatible with the Niinimaki study findings. There was no difference in major adverse events as defined by the authors (emergency department visit, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion) between the groups. The authors conclude medical and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

The 2018 Carlsson study is addressed above in section II.A.2.b.ii. of this response; as discussed above, that study showed no statistically significant difference between the overall complication rates between an "at home" and "at the hospital" abortion.[125]

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical abortion. However, as noted above, in the vast majority of medical abortions, surgical intervention is not necessary. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. Patients and their healthcare providers should discuss which method is preferable and safer according to each woman's unique situation.

You state that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13-14). As we explain below, additional studies are not needed at this time.

In justifying your assertion that a formal study is required in patients under the age of 18, you state that Mifeprex was approved for use in the pediatric population in 2000 after the requirement for studies in the pediatric population was waived (Petition at 13-14). The approved indication for mifepristone does not limit its use by age. Although patients age 17 and under were not included in the clinical trials supporting the initial approval of Mifeprex in 2000, we stated at the time that the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents. Our conclusion in 2000 that pediatric studies of Mifeprex were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time. Because we determined that there were sufficient data from studies of mifepristone, the original Mifeprex approval should have reflected the Agency's conclusion that the pediatric study requirements were waived for pre-menarchal females and that the pediatric study requirements were met for post-menarchal adolescents, rather than stating that the Agency was waiving the requirements for all pediatric age groups.

As currently required by the Pediatric Research Equity Act (PREA),[126] certain applications or supplemental applications must include pediatric assessments of the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric

[125] Carlsson et al., supra n. 49.
[126] Section 505B of the FD&C Act (21 U.S.C. 355c).

subpopulations, unless that requirement is waived or deferred.[127] In accordance with PREA, when FDA reviewed the S-020 efficacy supplement, a partial waiver was granted for pediatric studies in pre-menarchal females because pregnancy does not occur in premenarchal females. We also determined that the applicant had fulfilled the pediatric study requirement in post-menarchal adolescents. This determination was based on data extrapolated from adults and information in literature. Review of these findings found the safety and efficacy in this population to be similar to the safety and efficacy in the adult population.[128] Therefore, we do not agree that a formal study is required in patients under 18.

With regard to your concerns about repeat abortions and your assertion that a study is necessary in this population, we acknowledge that published data concerning adverse reproductive health outcomes in U.S. women who undergo repeat medical abortions are limited. We concluded in our 2016 review of the S-020 efficacy supplement that there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. We also noted that return to fertility after the use of mifepristone is well documented. [129] This is reflected both in Section 17 of the approved labeling, Patient Counseling Information, which states that the provider should "inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses," and in the Medication Guide, which states "You can become pregnant again right after your pregnancy ends." Although you state that more than one out of every three abortions in the United Sates is a repeat abortion (Petition at 14),[130] we are not aware of reports suggesting greater safety concerns in repeat abortions than a first-time abortion. Therefore, we do not agree that a study is necessary in this population. You also cite a published study, using a mouse model, of repeated medical termination of pregnancy that showed repeat medical abortion impaired the reproductive function of female mice (Petition at 14).[131] Per our 2016 review, there is no evidence in available clinical data that repeated medical or surgical abortion is unsafe, or that fertility is impaired by the use of mifepristone; therefore, data from a single non-clinical study in mice are not persuasive.[132]

With respect to your request for a formal study of mifepristone for medical abortion in women without access to emergency care, we disagree that such a study is necessary. In order to become a certified prescriber, a healthcare provider must agree that they have the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others, and that they have the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. These prescriber qualifications ensure that mifepristone is prescribed to women for whom emergency care is available.

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[127] Section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2)).
[128] 2016 Clinical Review, supra n. 13, at 74-76.
[129] Id. at 47.
[130] In support of this assertion, you cite Jones R, Jerman J, Ingerick M. Which abortion patients have had a prior abortion? Findings from the 2014 U.S. Abortion Patient Survey. J Womens Health.
[131] Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. PLoS One. 2012;7(10):e48384. doi:10.1371/journal.pone.0048384.
[132] 2016 Clinical Review, supra n. 13, at 47.

Finally, you assert that FDA should require a formal study in patients who self-administer misoprostol. As explained in section II.A.2.b.ii of this response, FDA conducted a literature review of self-administration of misoprostol at home as part of its review of the S-020 efficacy supplement and found no safety or efficacy concerns with home self-administration of misoprostol. Therefore, we disagree that a formal study is required in this population.

With regard to safety generally, in addition to the FAERS data provided above (see section II.B.1.c.ii. in this response), FDA routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy through 70 days gestation. We have not identified any new safety concerns with the use of mifepristone for this indication.

3. Other Articles

In your Petition, you reference several documents that discuss alternative models of providing abortion medications and advocate for the lifting of the REMS on mifepristone (Petition at 23-24). You assert that these recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex.[133]
We agree that the overarching message in the publications you reference appears to be advocating self-management of medical abortion. Nonetheless, as discussed in this response, we have determined that the Mifepristone REMS Program continues to be necessary for the safe use of this drug product, with some modifications.

III. CONCLUSION

For the reasons set forth above, we deny your request that FDA restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000; and we grant in part and deny in part your request to retain the Mifepristone REMS Program. As with all approved drug products, we will continue to monitor the safety of mifepristone for the approved indication and take any appropriate actions.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2021.12.16 15:05:41 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[133] You also reference clinical trials relating to the use of mifepristone for spontaneous miscarriage management and question the results of studies related to this use (Petition at 16-18). The use of mifepristone for the management of early miscarriage is not an approved indication for this drug product and is outside the scope of the Mifepristone REMS Program. Therefore, we do not address it in this response.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

v.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIVIL ACTION

Case No. 1-:17-cv-00493-JAO-RT

CERTIFICATE OF SERVICE

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on March 30, 2023, true and correct copies of the foregoing documents were electronically transmitted to the Clerk's Office using the CM/ECF System, which will send notification of such filing to all counsel of record.

DATED: Honolulu, Hawaii, March 30, 2023.

/s/ Jongwook "Wookie" Kim
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