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IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF HAWAII

GRAHAM T. CHELIUS, M.D., *et al.*, Plaintiffs, v. XAVIER BECERRA, *et al.*, Defendants.	CIV. NO. 1:17-00493-JAO-RT **DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION TO COMPLETE OR, IN THE ALTERNATIVE, SUPPLEMENT THE RECORD**

TABLE OF CONTENTS

INTRODUCTION 1
BACKGROUND 3
I. Statutory and regulatory background 3
II. Factual background 5
A. The Mifepristone REMS Program 5
B. ACOG's Citizen Petition 11
ARGUMENT 12
I. The Court should deny Plaintiffs' motion to complete the record 12
II. The Court should deny Plaintiffs' motion to supplement the record with extra-record evidence 19
CONCLUSION 25

TABLE OF AUTHORITIES

Cases

Alegre v. United States,
No. 16-CV-2442-AJB-KSC, 2021 WL 4934982
(S.D. Cal. July 29, 2021) 13, 15, 17

Am. Coll. of Obstetricians & Gynecologists v. FDA,
472 F. Supp. 3d 183 (D. Md. 2020) 9

Blue Mountains Biodiversity Project v. Jeffries,
72 F.4th 991 (9th Cir. 2023) 12, 13, 14, 15, 17, 21

Conservation Cong. v. U.S. Forest Serv.,
No. 2:13-CV-01922-TLN-CMK, 2016 WL 10637090
(E.D. Cal. Oct. 12, 2016) 13, 14, 15, 16, 17

Cook Inletkeeper v. EPA,
400 F. App'x 239 (9th Cir. 2010) 20

CoreCivic, Inc. v. Candide Grp., LLC,
46 F.4th 1136 (9th Cir. 2022) 14

Ctr. for Biological Diversity v. Jewell,
CV-12-02296-PHX-DGC, 2014 WL 116408
(D. Ariz. Jan. 13, 2014) 21, 22, 24

Detroit Int'l Bridge Co. v. Gov't of Canada,
No. CV 10-476 (RMC), 2016 WL 10749142 (D.D.C. Apr. 25, 2016) 16

FDA v. Am. Coll. of Obstetricians & Gynecologists,
141 S. Ct. 578 (2021) 9, 10, 11, 12

Fence Creek Cattle Co. v. U.S. Forest Serv.,
602 F.3d 1125 (9th Cir. 2010) 19, 20

Goffney v. Becerra,
995 F.3d 737 (9th Cir. 2021) 14, 15

High Sierra Hikers Association v. U.S. Dep't of the Interior,
No. C-09-4621 JCS, 2011 WL 2531138 (N.D. Cal. June 24, 2011) 25

Lands Council v. Powell,
395 F.3d 1019 (9th Cir. 2005) 20, 21, 25

Nw. Env't Advocs. v. U.S. Fish & Wildlife Serv.,
No. 3:18-CV-01420-AC, 2019 WL 6977406 (D. Or. Dec. 20, 2019) 20, 21

Organic Pastures Dairy Co. v. Sebelius,
No. 1:12-CV-02019-SAB, 2013 WL 4648548
(E.D. Cal. Aug. 29, 2013)..... 21, 22, 24

Pac. Shores Subdivision v. U.S. Army Corps of Eng'rs,
448 F. Supp. 2d 1 (D.D.C. 2006) 13, 18

Portland Audubon Society v. Endangered Species Committee,
984 F.2d 1534 (9th Cir. 1993).....14

Safari Club Int'l v. Jewell,
No. CV-16-00094-TUC-JGZ, 2016 WL 7785452
(D. Ariz. July 7, 2016)..... 12, 13, 16, 17, 25

Thompson v. U.S. Dep't of Lab.,
885 F.2d 551 (9th Cir. 1989)..... 12, 14, 17, 18

Trout Unlimited v. Lohn,
No. C05-1128C, 2006 WL 1207901 (W.D. Wash. May 4, 2006) 25

Washington v. FDA,
No. 1:23-CV-3026-TOR, 2023 WL 2825861 (E.D. Wash. Apr. 7, 2023).....22

Whole Woman's Health All. v. FDA,
No. 3:23-CV-00019, 2023 WL 5401885 (W.D. Va. Aug. 21, 2023) 22

WildEarth Guardians v. U.S. Fish & Wildlife Serv.,
No. CV-13-00151-TUC-RCC, 2015 WL 13567455
(D. Ariz. Sept. 28, 2015) 20

Xerces Soc'y for Invertebrate Conservation v. Shea,
No. 3:22-CV-00790-HZ, 2023 WL 4941221 (D. Or. July 17, 2023) 16

Statutes

5 U.S.C. §
702 12
706 ..... 12, 13, 16

21 U.S.C. §
331 4
355(a).....3
355(d).....3
355-1 4
355-1(f)(1) 4

355-1(f)(2) 4
355-1(f)(3) 4
355-1(g)(4) 4
355-1(g)(4)(B) 4

Pub. L. No. 110-85 §
901 3
909 4
909(b)(1) 5

Regulations

21 C.F.R. §
314.50 3
314.70 3
314.105(c) 3
314.520 3

42 C.F.R. §
405.1042(a)(2) 14

Other Authorities

Final Rule, 57 Fed. Reg. 58,942 (Dec. 11, 1992) 3

INTRODUCTION

Plaintiffs challenge the Food and Drug Administration's January 2023 approval of supplemental new drug applications that modified the restrictions in the Mifepristone Risk Evaluation and Mitigation Strategy (REMS) Program for the approved use of mifepristone: medical termination of intrauterine pregnancy through 70 days gestation. On September 29, 2023, Defendants certified the index of the administrative record for the challenged decision and completed production of the record, which spans over 6,000 pages. Ex. E.[1] Plaintiffs now seek to complete or, in the alternative, supplement that record with additional documents: a Citizen Petition submitted to FDA in October 2022 by the American College of Obstetricians and Gynecologists (ACOG) and 48 other organizations, the documents that the petition lists as references, and FDA's denial of that petition in January 2023 (collectively, the "ACOG Citizen Petition documents").[2] But these

[1] Citations to lettered exhibits refer to the exhibits to Plaintiffs' Motion to Complete or, in the Alternative, Supplement the Record, ECF No. 198. Citations to numbered exhibits refer to the exhibits to the Declaration of Isaac C. Belfer, attached to this brief.

[2] As it happens, seven of the documents that the petition lists as references are already in the record, because they were retrieved in response to FDA's literature search for the REMS review or because a submission that fell within the scope of FDA's REMS review listed them as a reference: Reference 3 (Ex. 1), Reference 5 (Ex. 2), Reference 23 (Ex. 3), Reference 37 (Ex. 4), Reference 44 (Ex. 5), Reference 47 (Ex. 6), and Reference 49 (Ex. 7). Any dispute over those documents is moot.

documents are not properly part of the record because FDA's denial of the ACOG petition is not challenged here, and the petition was not directly or indirectly considered by FDA when reaching the separate decision to approve the modification to the Mifepristone REMS Program. While ACOG's petition addressed an unapproved use of mifepristone for miscarriage management, FDA's REMS review concerned a different issue: the REMS for the *approved* indication of mifepristone for medical termination of early pregnancy. Plaintiffs have not come close to meeting their burden to present clear evidence that the record compiled by the agency omits documents that the decisionmaker actually considered.

Nor have Plaintiffs cleared the high bar to supplement the record with their extra-record evidence. Plaintiffs argue this extra-record evidence is necessary to determine whether the agency considered all relevant factors. But courts construe this exception to the record-review rule narrowly, applying it only when the agency failed to consider a general subject that was relevant to the decision. Here, while the ACOG petition discussed whether the then-existing REMS requirements were unduly burdensome for the unapproved use of mifepristone for miscarriage management, miscarriage management was not relevant to FDA's review of the burdens of the REMS on patient access for mifepristone's approved use. Moreover, FDA thoroughly considered whether the REMS requirements were unduly

burdensome with respect to that approved use. Thus, supplementation of the record is not warranted.

BACKGROUND

I. Statutory and regulatory background

The Federal Food, Drug, and Cosmetic Act (FDCA) generally prohibits the interstate distribution of new drugs that have not received FDA approval. 21 U.S.C. § 355(a). FDA approves a new drug application if the drug is shown to be safe and effective for its intended use(s). *Id.* § 355(d); *see also* 21 C.F.R. §§ 314.50, 314.105(c). Similarly, when a drug's sponsor proposes changes to the drug's conditions of approval (such as changes to labeling or to restrictions relating to its distribution or use), FDA reviews the scientific evidence submitted in support of the proposal to determine if it should be approved. *See* 21 C.F.R. § 314.70.

In 1992, FDA promulgated regulations (the Subpart H regulations) providing for the imposition of conditions "needed to assure safe use" of certain new drugs that satisfy the other requirements for approval under the FDCA. Final Rule, 57 Fed. Reg. 58,942, 58,958 (Dec. 11, 1992) (codified at 21 C.F.R. § 314.520). In the Food and Drug Administration Amendments Act of 2007, Congress codified and expanded the Subpart H regulations by giving FDA authority to require a REMS when it determines that restrictions are necessary to ensure that the benefits of a drug outweigh the risks. *See* Pub. L. No. 110-85, tit. IX, § 901 (codified at, *inter*

alia, 21 U.S.C. § 355-1). FDA may require that a REMS include "elements to assure safe use," such as a requirement that a drug's prescribers have particular training or that a drug be dispensed only in certain settings. *See* 21 U.S.C. § 355-1(f)(1)–(3).

The 2007 statute expressly incorporated drugs with existing Subpart H restrictions into the new REMS framework. *See* Pub. L. No. 110-85, tit. IX, § 909 (21 U.S.C. § 331 note). Specifically, Congress "deemed" such drugs to have a REMS in effect, with the Subpart H restrictions serving as "elements to assure safe use." *Id.* § 909(b). Thereafter, sponsors for such drugs were required to submit supplemental drug applications with a proposed REMS, which FDA then reviewed. *See id.*

The 2007 statute also provided standards for modifying an existing REMS. *See* 21 U.S.C. § 355-1(g)(4). As relevant here, FDA may require an applicant to "submit a proposed modification" to the REMS if the agency "determines that 1 or more goals or elements should be added, modified, or removed" from the approved REMS to "ensure the benefits of the drug outweigh the risks of the drug" or "minimize the burden on the health care delivery system of complying with the strategy." *Id.* § 355-1(g)(4)(B).

II. Factual background

A. The Mifepristone REMS Program

In 2000, FDA approved mifepristone (under the brand name Mifeprex) in a regimen with misoprostol for medical termination of intrauterine pregnancy through 49 days gestation. At the same time, to assure mifepristone's safe use, FDA placed Subpart H restrictions on the distribution and use of the drug product, including that (1) patients sign a Patient Agreement Form; (2) prescribers certify that (among other things) they have the ability to accurately date pregnancies and diagnose ectopic pregnancies, and will either perform surgical intervention or arrange for others to perform it if necessary; and (3) the drug be dispensed in person in certain healthcare settings, by or under the supervision of a specially certified prescriber. Ex. 8. FDA concluded based on a review of clinical trials and other scientific evidence that, under those conditions, mifepristone was safe and effective to terminate early pregnancy.

Because these Subpart H restrictions were in place when the 2007 statute took effect, Mifeprex was "deemed to have in effect an approved [REMS]" that continued these restrictions as "elements to assure safe use." Pub. L. No. 110-85, § 909(b)(1); *see also* Ex. 9. In 2011, in response to a submission by the sponsor, FDA approved the Mifeprex REMS after determining that it remained necessary to ensure the benefits of mifepristone outweigh the risks. Supplement Approval for

NDA 020687/S-014 (June 8, 2011), https://perma.cc/JJJ9-NYKQ. When FDA approved a generic version of the drug in 2019, it approved a single, shared system REMS, known as the Mifepristone REMS Program, for both Mifeprex and the generic version. Ex. 10.

FDA has since reviewed and approved modifications to the Mifepristone REMS Program that are consistent with decades of experience reflecting that the benefit-risk profile for the approved use of mifepristone remains favorable.[3] As relevant here, on May 7, 2021, FDA announced that it would review the elements of the Mifepristone REMS Program to determine whether those elements should be modified. Ex. 12 at 2023 SUPP 001368. FDA's review encompassed "multiple different sources of information," including "published literature," "safety information," adverse event reports, a "REMS assessment report" submitted by the applicants, and "information provided by advocacy groups, individuals, and the [sponsors]." *Id.* at 2023 SUPP 001370. The agency's literature review covered material published between March 29, 2016 (the date of an earlier REMS modification) and July 26, 2021, and included publications found on PubMed and Embase as well as those provided by "advocacy groups, individuals, plaintiffs in [*Chelius v. Becerra*, Civ. No. 1:17-00493-JAO-RT (D. Haw.)]," the sponsors, and

[3] *See, e.g.*, Ex. 11 at FDA 0374 (modifying REMS and extending approved use through 70 days gestation); https://perma.cc/7BQC-AJP9 (see Approval Date(s) and History, Letters, Labels, Reviews for NDA 020687).

"healthcare providers and researchers." *Id.* at 2023 SUPP 001370–71.

On December 16, 2021, FDA announced its conclusion that "the Mifepristone REMS Program continues to be necessary to ensure the benefits [of mifepristone] outweigh the risk[s]" and that "certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone." Ex. 13 at 2019 CP 000634. Specifically, FDA found that the prescriber certification and Patient Agreement Form requirements continued to be necessary. *Id.* at 2019 CP 000650. At the same time, FDA determined that the REMS "must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings . . . because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks." *Id.* at 2019 CP 000653. FDA also determined that because the in-person dispensing requirement was being removed, it was necessary to add a new requirement that pharmacies that dispense the drug be certified. *Id.* at 2019 CP 000663. "[M]ifepristone will remain safe and effective" with these REMS modifications, FDA concluded, "provided all the other requirements of the REMS are met." *Id.*

FDA detailed its reasoning in a 49-page scientific review memorandum. Ex. 12. *First*, FDA explained that it was retaining the prescriber certification requirement, under which mifepristone can be prescribed only by providers who are certified under the REMS and attest, among other things, that they can

accurately date pregnancies, diagnose ectopic pregnancies, and perform or arrange for surgical intervention for patients who experience complications. *Id.* at 2023 SUPP 001372–74. The agency concluded that prescriber certification "continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks," but noted that "[t]he burden of prescriber certification has been minimized to the extent possible" because each provider need only provide one certification to each of the two drug sponsors for mifepristone. *Id.* at 2023 SUPP 001374.

Second, FDA concluded that "literature that focused on the informed consent process" "d[id] not provide evidence that would support removing" the Patient Agreement Form requirement. *Id.* at 2023 SUPP 001376–77. Among other things, the agency found that the single-page Patient Agreement Form "is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients," "does not impose an unreasonable burden on providers or patients," and "remains necessary to assure the safe use of Mifepristone." *Id.* at 2023 SUPP 001378.

Third, based on an extensive review of the REMS assessment reports submitted by the drug's sponsors, postmarketing safety data (including adverse event data), and the published literature, *id.* at 2023 SUPP 001378–1400, FDA found the in-person dispensing requirement was no longer necessary to assure the

safe use of the drug. For much of the COVID-19 public health emergency, FDA had not enforced the in-person dispensing requirement.[4] Based on the agency's review of data from the public health emergency and other information, FDA found that "there does not appear to be a difference in adverse events between periods during the COVID-19 [public health emergency] when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced." *Id.* at 2023 SUPP 001398. Moreover, postmarketing data did not show any new safety concerns with use of the drug. *Id.* The published literature also supported the agency's determination. *Id.* at 2023 SUPP 001384–96. The agency therefore 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." *Id.* at 2023 SUPP 001399.

The pharmacy certification requirement permits pharmacies to dispense mifepristone upon prescriptions by certified prescribers if the pharmacies become

[4] In July 2020, a district court preliminarily enjoined enforcement of that requirement in light of the public health emergency. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. 2020). Although the Supreme Court eventually stayed that preliminary injunction in January 2021, *see FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (2021) (mem.), FDA announced in April 2021 that it would exercise enforcement discretion with respect to the in-person dispensing requirement during the public health emergency. *See* Ex. 1.

certified by agreeing to follow applicable REMS requirements. FDA expressly tied the addition of the pharmacy certification requirement to the removal of the in-person dispensing requirement. *See id.* at 2023 SUPP 001400 ("Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies . . . ."). Adding this requirement would "incorporate[] pharmacies into the REMS, ensur[ing] that [they] are aware of and agree to follow applicable REMS requirements, and . . . that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers." *Id.* "Without pharmacy certification," FDA explained, "a pharmacy might dispense product that was not prescribed by a certified prescriber." *Id.* Consequently, 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," FDA determined that the Mifepristone REMS Program must be modified to "remov[e] the in-person dispensing requirement" and add the "requirement for pharmacy certification." *Id.* at 2023 SUPP 001401.

FDA directed the drugs' sponsors to submit supplemental applications proposing these modifications to the REMS. Ex. 14; Ex. 15. The sponsors submitted their supplemental applications in 2022, and FDA approved them on January 3, 2023. Ex. 16 at 2023 SUPP 001120–26; Ex. 17; Ex. 19.

B. ACOG's Citizen Petition

On October 4, 2022, ACOG submitted a Citizen Petition to FDA on behalf of itself and 48 other organizations. Ex. A at 1. The petition requested that FDA ask Danco Laboratories, LLC (Danco)—the sponsor of Mifeprex (mifepristone)—to submit a Supplemental New Drug Application (sNDA) "to add miscarriage management as an indication to the mifepristone label and to modify the REMS so that it does not unduly burden its use for miscarriage management." *Id.* at 2. The petition also requested that, while FDA "is considering these changes," it "state that it will exercise enforcement discretion with respect to the use and distribution of mifepristone consistent with the requested indication and REMS modifications." *Id.*

On January 3, 2023, FDA denied ACOG's Citizen Petition. Ex. C at 1. First, FDA denied ACOG's "request that [FDA] ask the [Mifeprex sponsor] to submit an sNDA that seeks to add miscarriage management as an indication to the drug's labeling." *Id.* at 3. FDA explained that "[o]nly the holder of an approved application may submit a supplement to an application." *Id.* FDA next denied ACOG's request that FDA "eliminate or modify the Mifepristone REMS Program so that it is not unduly burdensome for a miscarriage management indication." *Id.* at 4. The agency explained that "[b]ecause the management of miscarriage is not a currently approved indication for mifepristone, it would be premature for FDA to

consider the impact that the addition of this indication would have, if any, on the Mifepristone REMS Program so that it is not unduly burdensome for that use." *Id.* Finally, FDA denied ACOG's request that "FDA immediately exercise enforcement discretion with respect to the use and distribution of mifepristone for miscarriage management without complying with the Mifepristone REMS Program." *Id.* Under its regulations, FDA explained, "[a]gency decisions to take, or to refrain from taking, enforcement action . . . are not properly the subject of a citizen petition." *Id.*

ARGUMENT

I. The Court should deny Plaintiffs' motion to complete the record

Judicial review of an "agency action" under the Administrative Procedure Act (APA) is based on "the whole record," 5 U.S.C. §§ 702, 706, which consists of "all documents and materials directly or indirectly considered by agency decision-makers" in reaching the particular decision under review, *Blue Mountains Biodiversity Project v. Jeffries*, 72 F.4th 991, 996 (9th Cir. 2023) (quoting *Thompson v. U.S. Dep't of Lab.*, 885 F.2d 551, 555 (9th Cir. 1989)) (internal quotation marks omitted). "Documents and materials indirectly considered by agency decision-makers are those that may not have literally passed before the eyes of the decision-makers, but were so heavily relied on in [subordinates'] recommendation[s]" or in other materials directly considered by the decisionmaker "that the decision maker constructively considered them." *Safari Club Int'l v.*

Jewell, No. CV-16-00094-TUC-JGZ, 2016 WL 7785452, at *2 (D. Ariz. July 7, 2016) (quotations omitted).

The "whole record," 5 U.S.C. § 706, "is ordinarily the record the agency presents," *Blue Mountains Biodiversity Project*, 72 F.4th at 996 (quotations omitted). After all, the agency "did the considering" and "therefore is in a position to indicate initially which of the materials were before it—namely, were directly or indirectly considered." *Pac. Shores Subdivision v. U.S. Army Corps of Eng'rs*, 448 F. Supp. 2d 1, 5 (D.D.C. 2006) (quotations omitted).

"[L]ike other official agency actions, an agency's statement of what is in the record is subject to a presumption of regularity." *Blue Mountains Biodiversity Project*, 72 F.4th at 997 (quotations omitted). Specifically, the Ninth Circuit has instructed courts to "presume that an agency properly designated the Administrative Record" absent "clear evidence to the contrary." *Id.* (quotations omitted). Thus, to rebut the presumption of regularity, a party must show by clear evidence that the proffered documents were considered by the agency in reaching the challenged decision. *See Alegre v. United States*, No. 16-CV-2442-AJB-KSC, 2021 WL 4934982, at *4 (S.D. Cal. July 29, 2021); *Conservation Cong. v. U.S. Forest Serv.*, No. 213CV01922TLNCMK, 2016 WL 10637090, at *2 (E.D. Cal. Oct. 12, 2016). This standard is met only in "rare cases," and mere "inference[s]" about what the agency considered are not enough. *Conservation Cong.*, 2016 WL

10637090, at *2, *4.

Plaintiffs cite the statement in *Portland Audubon Society v. Endangered Species Committee*, 984 F.2d 1534 (9th Cir. 1993), that "'[t]he whole record' includes everything that was before the agency pertaining to the merits of its decision." *Id.* at 1548; *see* ECF No. 198, Mot., at 2, 10. That is simply another articulation of the "directly or indirectly considered" standard previously set out in *Thompson*, and indeed *Portland Audubon Society* cited *Thompson*. 984 F.2d at 1548 (citing *Thompson,* 885 F.2d at 555–56). Moreover, even if there were a substantive difference between the language in *Portland Audubon Society* and *Thompson*, *Thompson* would control. *See CoreCivic, Inc. v. Candide Grp., LLC*, 46 F.4th 1136, 1141 (9th Cir. 2022). The Ninth Circuit recently confirmed the continued vitality of *Thompson*'s "directly or indirectly considered" standard. *See Blue Mountains Biodiversity Project*, 72 F.4th at 996 (citing *Thompson*, 885 F.2d at 555).

Similarly, the Ninth Circuit did not change the "directly or indirectly considered" standard in *Goffney v. Becerra*, 995 F.3d 737 (9th Cir. 2021)—nor could it have, *see CoreCivic*, 46 F.4th at 1141. *Goffney* observed that this standard was "codified" in a regulation specifying that the record of an adjudication by an Administrative Law Judge included, among other things, "proffered evidence excluded by the adjudicator." 995 F.3d at 747 (citing 42 C.F.R. § 405.1042(a)(2));

see Mot. 13. The court did not say that scope was identical to the scope of the record under Ninth Circuit precedent, and in the same paragraph it quoted *Thompson*'s "directly or indirectly considered" standard. *Goffney*, 995 F.3d at 747.[5]

Plaintiffs here have not met their burden to show by clear evidence that the record fails to include documents or materials that the agency "actually considered when making [the challenged] decision." *Conservation Cong.*, 2016 WL 10637090, at *2; *see Blue Mountains Biodiversity Project*, 72 F.4th at 996–97; *Alegre*, 2021 WL 4934982, at *4. FDA's denial of ACOG's Citizen Petition is not the decision challenged in this case. And Plaintiffs have not provided *any* evidence, let alone clear evidence, that in deciding to approve the January 2023 modification to the Mifepristone REMS Program, the agency decisionmaker "actually considered" the ACOG Citizen Petition documents, either directly or indirectly. *Conservation Cong.*, 2016 WL 10637090, at *2; *see Blue Mountains Biodiversity Project*, 72 F.4th at 996–97; *Alegre*, 2021 WL 4934982, at *4. Specifically, Plaintiffs have not shown that the decisionmaker directly considered those materials, nor have they shown that the materials "were so heavily relied on in

[5] Plaintiffs argue that "the record already contains numerous studies that FDA expressly excluded from its REMS review." Mot. 12–13. To be clear, FDA stated that it "excluded from the REMS review" certain "References Cited in Letters from [the *Chelius*] Plaintiffs," meaning that it considered those references but did not rely on them, for the reasons explained in its memorandum. Ex. 12 at 2023 SUPP 001405–09.

[subordinates'] recommendation[s]" or in other materials directly considered by the decisionmaker "that the decision maker constructively considered them." *Safari Club Int'l*, 2016 WL 7785452, at *2 (quotations omitted).

At most, Plaintiffs argue that "FDA received the Petition on October 4, 2022," prior to completing its REMS review on January 3, 2023, and that "the Petition was relevant to the challenged agency action." Mot. 11–12. As an initial matter, although the ACOG petition concerned mifepristone, its requests were not relevant to the REMS review because they pertained to an unapproved use of mifepristone for miscarriage management, whereas the REMS review concerned the approved use of mifepristone for termination of early pregnancy. Moreover, the mere "fact that the agency possessed the documents prior to the [challenged] decision does not mean that they were 'before the agency' for purposes of judicial review under . . . 5 U.S.C. § 706." *Detroit Int'l Bridge Co. v. Gov't of Canada*, No. CV 10-476 (RMC), 2016 WL 10749142, at *2 (D.D.C. Apr. 25, 2016); *see Conservation Cong.*, 2016 WL 10637090, at *2 (plaintiffs "cannot succeed simply by showing that the agencies were aware of [a document] or had [it] somewhere in their possession"). Plaintiffs cannot "simply assert[] that the documents were relevant, were before or in front of the agency and not included in the record." *Xerces Soc'y for Invertebrate Conservation v. Shea*, No. 3:22-CV-00790-HZ, 2023 WL 4941221, at *5 (D. Or. July 17, 2023) (alteration in original) (quotations omitted);

see Alegre, 2021 WL 4934982, at *4.

Courts should "be cautious against permitting the admission of any relevant document contained in the agency's filing cabinet," which would "fail[] to give appropriate deference to the agency's designation" of the documents it directly or indirectly considered. *Safari Club Int'l*, 2016 WL 7785452, at *2 (quotations omitted). This Court should not throw caution to the wind when Plaintiffs have failed to meet their burden to show by clear evidence that the record fails to include materials considered by the agency in reaching the challenged decision. *See Blue Mountains Biodiversity Project*, 72 F.4th at 996–97; *Alegre*, 2021 WL 4934982, at *4; *Conservation Cong.*, 2016 WL 10637090, at *2.

The Ninth Circuit's decision in *Thompson* does, as Plaintiffs suggest, help dispose of this motion, *see* Mot. 12—but in Defendants' favor. In *Thompson*, an employee filed complaints against his employer with the Department of Labor. 885 F.2d at 553. After the parties reached a settlement, the agency dismissed the employee's complaints with prejudice. *Id.* at 554. The employee moved for reconsideration, arguing that his complaints should not have been dismissed with prejudice and submitting settlement correspondence in support. *Id.* The agency denied the employee's reconsideration motion. *Id.* at 555. On appeal, the Ninth Circuit held the settlement correspondence was part of the record because it was "considered by the Secretary, either directly or indirectly," in denying the

employee's reconsideration motion. 885 F.2d at 555–56. Importantly, the settlement correspondence was submitted to the agency as part of the very reconsideration proceedings being challenged in court.

By contrast here, the review process that led to the approval of the January 2023 modification to the Mifepristone REMS Program was distinct from the review and denial of the ACOG Citizen Petition. The Citizen Petition concerned the unapproved use of mifepristone for miscarriage management. For example, it requested FDA to ask Danco to submit an sNDA "to add miscarriage management as an indication to the mifepristone label and to modify the REMS so that it does not unduly burden its use for miscarriage management." Ex. A at 2. It argued that mifepristone "is the most effective regimen for medical management of miscarriage" and that the REMS "is unnecessary to ensure mifepristone's benefits for miscarriage management outweigh its risks," *id.* at 7, 11–12. Although certain statements in the petition were phrased broadly and not expressly limited to the use of mifepristone for miscarriage management, *e.g.*, *id.* at 12; *see* Mot. 12, those statements were made in support of arguments that unambiguously concerned that unapproved use.

Miscarriage management, however, was outside the scope of FDA's review of the burdens related to mifepristone's approved use. *See* Ex. 12 at 2023 SUPP 001371 (FDA excluded "[s]afety data related to mifepristone use for spontaneous

first trimester abortion (i.e., miscarriages)" because "[t]hese publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation."). As FDA explained in a consult for a March 29, 2019 Citizen Petition, "[t]he use of mifepristone for the management of early miscarriages is investigational and outside the scope of the Mifepristone REMS Program." Ex. 18 at 2019 CP 000621; *see* Ex. C at 4 (denying ACOG's Citizen Petition because, among other reasons, "the management of miscarriage is not a currently approved indication for mifepristone"). Thus, unlike the facts of *Thompson*, the evidence shows FDA did not consider the ACOG Citizen Petition when deciding to approve the January 2023 modification to the Mifepristone REMS Program.[6]

II. The Court should deny Plaintiffs' motion to supplement the record with extra-record evidence

Just as Plaintiffs cannot show the record is incomplete, they cannot meet the threshold for supplementing the record with documents not considered by the decisionmaker. Plaintiffs first must meet a "heavy burden to show that the additional materials sought are necessary to adequately review the [agency]'s decision." *Fence Creek Cattle Co. v. U.S. Forest Serv.*, 602 F.3d 1125, 1131 (9th Cir. 2010); *see Nw. Env't Advocs. v. U.S. Fish & Wildlife Serv.*, No. 3:18-CV-

[6] That FDA responded to the ACOG Citizen Petition on the same day it approved the REMS modification, Mot. 12, does not mean FDA considered the petition in approving the REMS modification.

01420-AC, 2019 WL 6977406, at *8 (D. Or. Dec. 20, 2019). Plaintiffs next must show that their extra-record documents satisfy one of the "narrow exceptions to th[e] general rule" that "courts reviewing an agency decision are limited to the administrative record." *Lands Council v. Powell*, 395 F.3d 1019, 1029–30 (9th Cir. 2005). Plaintiffs fail to make either required showing.

Plaintiffs have failed to meet their "heavy burden to show that the [ACOG Citizen Petition documents] are necessary to adequately review [FDA]'s decision." *Fence Creek Cattle*, 602 F.3d at 1131; *see Nw. Env't Advocs.*, 2019 WL 6977406, at *8. The over-6,000 page administrative record, including the detailed, 49-page REMS Modification Rationale Review, Ex. 12, "contains sufficient information to explain how the [agency used the information before it] and why it reached its decision," *WildEarth Guardians v. U.S. Fish & Wildlife Serv.*, No. CV-13-00151-TUC-RCC, 2015 WL 13567455, at *3 (D. Ariz. Sept. 28, 2015) (quoting *Cook Inletkeeper v. EPA*, 400 F. App'x 239, 240–41 (9th Cir. 2010)).

Plaintiffs also have not shown that any of the "narrow exceptions" to the record-review rule applies. *Lands Council*, 395 F.3d at 1029–30. Plaintiffs rely on only one such exception: when extra-record evidence "is necessary to determine whether the agency has considered all relevant factors and has explained its decision." *Id.* at 1030. This exception is "narrowly construed and applied," *id.*, to prevent plaintiffs from "driv[ing] a truck through what is supposed to be a narrow

exception to the record review rule," *Nw. Env't Advocs.*, 2019 WL 6977406, at *9 (quotations omitted). It applies only when the agency "fail[ed] to consider a general subject matter that is demonstrably relevant to the outcome of the agency's decision, not when specific hypotheses and/or conclusions are omitted from consideration." *Ctr. for Biological Diversity v. Jewell*, No. CV-12-02296-PHX-DGC, 2014 WL 116408, at *2 (D. Ariz. Jan. 13, 2014) (quotations omitted); *see Organic Pastures Dairy Co. v. Sebelius*, No. 1:12-CV-02019-SAB, 2013 WL 4648548, at *5 (E.D. Cal. Aug. 29, 2013). It cannot be used "merely to bolster the record or supply background information." *Ctr. for Biological Diversity*, 2014 WL 116408, at *1.

Courts "place a thumb on the scale against supplementation" of the record. *Blue Mountains Biodiversity Project*, 72 F.4th at 998. "Were the federal courts routinely or liberally to admit new evidence when reviewing agency decisions," the Ninth Circuit cautioned, "it would be obvious that the federal courts would be proceeding, in effect, de novo rather than with the proper deference to agency processes, expertise, and decision-making." *Lands Council*, 395 F.3d at 1030.

Plaintiffs have failed to meet their burden to show that the ACOG Citizen Petition documents should be added to the record. Plaintiffs argue that FDA did not consider the Schummers study or "evidence in the Petition" allegedly showing that the then-existing REMS requirements were "unduly burdensome on patient

access." Mot. 14–15. But the ACOG petition discussed whether these requirements were unduly burdensome for *the unapproved use of mifepristone for miscarriage management*—a use not relevant to FDA's review of the mifepristone REMS to ensure the benefits of the drug outweigh its risks and to minimize the burden of complying with the REMS, with respect to the drug's approved use. *See Whole Woman's Health All. v. FDA*, No. 3:23-CV-00019, 2023 WL 5401885, at *6 (W.D. Va. Aug. 21, 2023) ("[t]he 2022 [ACOG] citizen petition is not directly relevant to the current action" challenging the Mifepristone REMS Program).[7] And even if there were "specific hypotheses and/or conclusions" in the ACOG Citizen Petition documents that were relevant and not considered in FDA's REMS review, Plaintiffs have not shown that FDA "fail[ed] to consider a general subject matter that is demonstrably relevant to the outcome of the agency's decision." *Ctr. for Biological Diversity*, 2014 WL 116408, at *2 (quotations omitted); *see Organic Pastures Dairy*, 2013 WL 4648548, at *5.

To the contrary, FDA thoroughly considered the "general subject matter" of

[7] Contrary to Plaintiffs' argument, Mot. 2, the court in *Washington v. FDA*, No. 1:23-CV-3026-TOR, 2023 WL 2825861, at *6 (E.D. Wash. Apr. 7, 2023), *opinion clarified*, No. 1:23-CV-3026-TOR, 2023 WL 2941567 (E.D. Wash. Apr. 13, 2023), did not find that the ACOG petition was relevant to the January 2023 REMS modification. Instead, the *Washington* court listed the ACOG petition, which it recognized focused on "miscarriage management," as one of several recent developments relating to the Mifepristone REMS Program that together showed that "administrative exhaustion through a citizen petition on the January 2023 REMS would be futile." *Id.*

whether the then-existing REMS requirements were unduly burdensome with respect to mifepristone's approved use. FDA considered information on this topic from "published literature, safety information collected during the COVID-19 [public health emergency], 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." Ex. 12 at 2023 SUPP 001396. For example, FDA compared safety data from periods when the in-person dispensing requirement was being enforced with safety data from periods when that requirement was not being enforced in light of the COVID-19 public health emergency, and found that "there does not appear to be a difference in adverse events between [those] periods." *Id.* at 2023 SUPP 001383; *see id.* at 2023 SUPP 001380–84. FDA also considered the Wiebe study providing safety and efficacy data on mifepristone use for "medical abortion with telemedicine consult" in Canada, though FDA found that "there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe) not generalizable to the US." *Id.* at 2023 SUPP 001385–86 (footnote omitted).

Based on this analysis, FDA determined, for example, that the Patient Agreement Form requirement "does not impose an unreasonable burden on

providers or patients." *Id.* at 2023 SUPP 001378. Also, "[t]he burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each [sponsor]." *Id.* at 2023 SUPP 001374. And "[r]emoving the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients." *Id.* at 2023 SUPP 001399. Thus, the evidence shows that FDA thoroughly considered whether the then-existing REMS requirements were unduly burdensome for mifepristone's approved use—the "general subject matter . . . demonstrably relevant to the outcome of the agency's decision" that Plaintiffs assert was addressed by the ACOG Citizen Petition documents. *Ctr. for Biological Diversity*, 2014 WL 116408, at *2 (quotations omitted); *see* Mot. 14–15; *Organic Pastures Dairy*, 2013 WL 4648548, at *5 (finding that FDA considered the general subject matter of "whether raw milk is deemed safe for human consumption" even though it did not "perform relative comparisons between raw milk and other food products").

Plaintiffs suggest that FDA should have considered Schummers because the agency had an abstract of the study when it issued the December 16, 2021, REMS Modification Rationale Review, and the full study was published in January 2022 and discussed in the ACOG petition. Mot. 14–15. But "courts have expressly rejected the use of the 'relevant factors' test as grounds for the admission of extra-record evidence where the plaintiff argues that the new evidence *should* have been

considered by the agency." *Safari Club Int'l*, 2016 WL 7785452, at *5 (emphasis in original).[8] Plaintiffs argue that it is enough that a document should have been considered, citing *High Sierra Hikers Association v. U.S. Department of the Interior*, No. C-09-4621 JCS, 2011 WL 2531138, at *8 (N.D. Cal. June 24, 2011), which in turn cited *Trout Unlimited v. Lohn*, No. C05-1128C, 2006 WL 1207901, at *3 (W.D. Wash. May 4, 2006). Mot. 11. However, *Trout Unlimited* failed to follow *Lands Council*'s holding that supplementation is proper only when a document meets one of the narrow exceptions to the record-review rule. *Compare* 2006 WL 1207901, at *4*, with Lands Council*, 395 F.3d at 1029–30. Thus, *Trout Unlimited* should not guide this Court's analysis.

CONCLUSION

For the foregoing reasons, the Court should deny Plaintiffs' Motion to Complete or, in the Alternative, Supplement the Record.

Dated: January 24, 2024

Respectfully submitted,

/s/ Isaac C. Belfer
NOAH T. KATZEN
ISAAC C. BELFER
Consumer Protection Branch
U.S. Department of Justice

[8] Moreover, in conducting a REMS review, the agency is not required to comb through references appended to a petition that requests action outside the scope of that review, to determine if any of those references contain information that might be relevant to that review.

Attorneys for Defendants Xavier Becerra, in his official capacity as Secretary, U.S. Department of Health and Human Services; U.S. Food and Drug Administration; and Robert M. Califf, in his official capacity as Commissioner of Food and Drugs

Certificate of Service

I hereby certify the foregoing document was served via ECF on all counsel of record on January 24, 2024.

/s/ Isaac C. Belfer

Isaac C. Belfer

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF HAWAII

GRAHAM T. CHELIUS, M.D., *et al.*, Plaintiffs, v. XAVIER BECERRA, *et al.*, Defendants.	CIV. NO. 1:17-00493-JAO-RT **DECLARATION OF ISAAC C. BELFER; EXHIBITS 1–19**

DECLARATION OF ISAAC C. BELFER

I, ISAAC C. BELFER, declare as follows:

1. I am a trial attorney in the Consumer Protection Branch, Civil Division, U.S. Department of Justice, and am representing Defendants Xavier Becerra, in his official capacity as Secretary of Health and Human Services; U.S. Food and Drug Administration; and Robert M. Califf, M.D., in his official capacity as Commissioner of Food and Drugs, in this case. The purpose of this declaration is to authenticate and enclose the exhibits cited in Defendants' Opposition to Plaintiffs' Motion to Complete or, in the Alternative, Supplement the Record.

2. Attached hereto as **Exhibit 1** is a true and correct copy of Letter from Janet Woodcock, Acting Commissioner, U.S. Food & Drug Admin. to Maureen G. Phipps, Chief Executive Officer, American College of Obstetricians and Gynecologists and William Grohman, President, Society for Maternal-Fetal

Medicine (Apr. 12, 2021), included in the administrative record in this case at Bates Numbers 2021 ED 000510–000511.

3. Attached hereto as **Exhibit 2** is a true and correct copy of Am. Coll. of Obstetricians & Gynecologists, Prac. Bull. No. 200, *Early Pregnancy Loss,* 132 Obstetrics & Gynecology e197–e207 (2018), included in the administrative record in this case at Bates Numbers 2021 REMS 000578–000588.

4. Attached hereto as **Exhibit 3** is a true and correct copy of Courtney A. Schreiber et al., *Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss,* 378 N. Eng. J. Med 2161–70 (2018), included in the administrative record in this case at Bates Numbers 2021 REMS 000568–000577.

5. Attached hereto as **Exhibit 4** is a true and correct copy of Review of proposed REMS modifications to Mifeprex (Mar. 29, 2016), included in the administrative record in this case at Bates Numbers FDA 0673–0709.

6. Attached hereto as **Exhibit 5** is a true and correct copy of Danielle Calloway et al., *Mifepristone restrictions and primary care: Breaking the cycle of stigma through a learning collaborative model in the United States,* 104 Contraception 24–28 (2021), included in the administrative record in this case at Bates Numbers 2021 REMS 000979–000983.

7. Attached hereto as **Exhibit 6** is a true and correct copy of 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, 2 Lancet Pub. Health e493–e500 (2017), included in the administrative record in this case at Bates Numbers 2021 REMS 001177–001184.

8. Attached hereto as **Exhibit 7** is a true and correct copy of Daniel Grossman et al., *Medication Abortion with Pharmacist Dispensing of Mifepristone,* 137 Obstetrics & Gynecology 613–22 (2021), included in the administrative record in this case at Bates Numbers 2021 REMS 000772–00781.

9. Attached hereto as **Exhibit 8** is a true and correct copy of Summary review memo (Sept. 28, 2000), included in the administrative record in this case at Bates Numbers FDA 0223–0230.

10. Attached hereto as **Exhibit 9** is a true and correct copy of Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16313 (Mar. 27, 2008), included in the administrative record in this case at Bates Numbers 2019 CP 000669–670.

11. Attached hereto as **Exhibit 10** is a true and correct copy of Approval Letter for SE-22 REMS Supplement for mifepristone, NDA 020687 (Apr. 11, 2019), included in the administrative record in this case at Bates Numbers 2023 SUPP 001180–001186.

12. Attached hereto as **Exhibit 11** is a true and correct copy of Approval package index and approval letter for Supp. 20 (Mar. 29, 2016), included in the administrative record in this case at Bates Numbers FDA 0371–0381.

13. Attached hereto as **Exhibit 12** is a true and correct copy of REMS Modification Rationale Review for mifepristone, NDA 020687 (Dec. 16, 2021), within the Danco Laboratories, LLC Approval Package for Application Number 020687Origls025, included in the administrative record in this case at Bates Numbers 2023 SUPP 001361–001410.

14. Attached hereto as **Exhibit 13** is a true and correct copy of Citizen Petition Response Letter from U.S. Food & Drug Admin. to American Association of Pro-Life Obstetricians & Gynecologists and American College of Pediatricians (Dec. 16, 2021), included in the administrative record in this case at Bates Numbers 2019 CP 000629–000668.

15. Attached hereto as **Exhibit 14** is a true and correct copy of Letter from U.S. Food & Drug Admin. to Danco Laboratories, LLC re: REMS Modification Notification (Dec. 16, 2021), included in the administrative record in this case at Bates Numbers 2021 REMS 001803–001807.

16. Attached hereto as **Exhibit 15** is a true and correct copy of Letter from U.S. Food & Drug Admin. to GenBioPro, Inc. re: REMS Modification

Notification (Dec. 16, 2021), included in the administrative record in this case at Bates Numbers 2021 REMS 001808–001811.

17. Attached hereto as **Exhibit 16** is a true and correct copy of Joint Summary Review (Jan. 3, 2023), included in the administrative record in this case at Bates Numbers 2023 SUPP 001112–001150.

18. Attached hereto as **Exhibit 17** is a true and correct copy of Letter from U.S. Food & Drug Admin. to Danco Laboratories, LLC re: Supplement Approval NDA 020687/S-025 (Jan. 3, 2023), included in the administrative record in this case at Bates Numbers 2023 SUPP 001448–001460.

19. Attached hereto as **Exhibit 18** is a true and correct copy of Citizen Petition Consult re: Actions Requested by Petitioners (Dec. 16, 2021), included in the administrative record in this case at Bates Numbers 2019 CP 000599–000627.

20. Attached hereto as **Exhibit 19** is a true and correct copy of Letter from U.S. Food & Drug Admin. to GenBioPro, Inc. re: Supplemental Approval ANDA 091178-S004 (Jan. 3, 2023), included in the administrative record in this case at Bates Numbers 2023 SUPP 001461–001465.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge.

Executed on January 24, 2024 at Washington, DC.

/s/ Isaac C. Belfer
ISAAC C. BELFER

Exhibit 1

U.S. FOOD & DRUG ADMINISTRATION

April 12, 2021

Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists
c/o Rachel Tetlow, Federal Affairs Director
rtetlow@acog.org

Skye Perryman, General Counsel
sperryman@acog.org

William Grobman, MD, MBA
President
Society for Maternal-Fetal Medicine
w-grobman@northwestern.edu

Dear Drs. Phipps and Grobman,

In your letter of April 20, 2020, to former Commissioner Stephen Hahn, you expressed concerns about the in-person dispensing requirements for certain prescription drugs during the current public health emergency. In my letter to you of March 19, 2021, I indicated that staff in the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) were evaluating the issues you raised.

Following up on my March 19, 2021, letter I am writing to report the results of CDER's review and analysis.

CDER conducted a literature search for studies pertinent to the in-person dispensing requirement in the Mifepristone REMS Program during the COVID-19 pandemic. Based on this literature search, CDER identified four publications that included relevant clinical outcome data.[1] CDER

[1] Chong E, et al. Expansion of a Direct-to-Patient Telemedicine Abortion Service in the United States and Experience during the COVID-19 Pandemic. Contraception 2021 (accepted manuscript). https://www.sciencedirect.com/science/article/pii/S0010782421000913; Kerestes C, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021 (accepted manuscript). https://doi.org/10.1016/j.contraception.2021.03.025; Aiken A et al. Effectiveness, Safety and Acceptability of No-test Medical Abortion Provided Via Telemedicine: a National Cohort Study. British J Obstet Gynecol 2021. https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.16668; Reynolds-Wright JJ et al. Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic. BMJ Sex Reprod Health 2021. https://srh.bmj.com/content/early/2021/02/04/bmjsrh-2020-200976

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Exhibit 1

found that although there are limitations to the study designs, the overall findings from these studies do not appear to show increases in serious safety concerns (such as hemorrhage, ectopic pregnancy, or surgical interventions) occurring with medical abortion as a result of modifying the in-person dispensing requirement during the COVID-19 pandemic.

CDER also reviewed postmarketing adverse events that reportedly occurred from January 27, 2020 - January 12, 2021, with mifepristone use for medical termination of early pregnancy, along with available information about deviations or noncompliance events associated with the Mifepristone REMS Program.[2] CDER found that the small number of adverse events reported to FDA during the COVID-19 public health emergency (PHE) provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to the reported adverse events.

In summary, provided the other requirements of the Mifepristone REMS Program are met, and given that the in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare personnel because it may involve a clinic visit solely for this purpose, CDER intends to exercise enforcement discretion during the COVID-19 PHE 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. Further, to the extent all of the other requirements of the Mifepristone REMS Program are met, CDER 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.

CDER is communicating this decision to the approved application holders subject to the Mifepristone REMS Program.

Sincerely yours,

Janet Woodcock, M.D.
Acting Commissioner of Food and Drugs

[2] See Mifepristone REMS Program at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390. CDER's analysis covers both products that are subject to the Mifepristone REMS Program (Mifeprex and the approved generic, Mifepristone Tablets, 200 mg).

Exhibit 2

INTERIM UPDATE

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 200

(Replaces Practice Bulletin Number 150, May 2015)

Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins Gynecology in collaboration with Sarah Prager, MD; Vanessa K. Dalton, MD, MPH; and Rebecca H. Allen, MD, MPH.

INTERIM UPDATE: This Practice Bulletin is updated as highlighted to reflect recent evidence regarding the use of mifepristone combined with misoprostol for medical management of early pregnancy loss. This Practice Bulletin also includes limited, focused updates to align with Practice Bulletin No. 181, *Prevention of Rh D Alloimmunization*.

Early Pregnancy Loss

Early pregnancy loss, or loss of an intrauterine pregnancy within the first trimester, is encountered commonly in clinical practice. Obstetricians and gynecologists should understand the use of various diagnostic tools to differentiate between viable and nonviable pregnancies and offer the full range of therapeutic options to patients, including expectant, medical, and surgical management. The purpose of this Practice Bulletin is to review diagnostic approaches and describe options for the management of early pregnancy loss.

Background

Definition

Early pregnancy loss is defined as a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity within the first 12 6/7 weeks of gestation (1). In the first trimester, the terms miscarriage, spontaneous abortion, and early pregnancy loss are used interchangeably, and there is no consensus on terminology in the literature. However, early pregnancy loss is the term that will be used in this Practice Bulletin.

Incidence

Early pregnancy loss is common, occurring in 10% of all clinically recognized pregnancies (2 4). Approximately 80% of all cases of pregnancy loss occur within the first trimester (2, 3).

Etiology and Risk Factors

Approximately 50% of all cases of early pregnancy loss are due to fetal chromosomal abnormalities (5, 6). The most common risk factors identified among women who have experienced early pregnancy loss are advanced maternal age and a prior early pregnancy loss (7, 8). The frequency of clinically recognized early pregnancy loss for women aged 20 30 years is 9 17%, and this rate increases sharply from 20% at age 35 years to 40% at age 40 years and 80% at age 45 years (7). Discussion of the many risk factors thought to be associated with early pregnancy loss is beyond the scope of this document and is covered in more detail in other publications (6, 7).

Clinical Considerations and Recommendations

▶ ***What findings can be used to confirm a diagnosis of early pregnancy loss?***

Common symptoms of early pregnancy loss, such as vaginal bleeding and uterine cramping, also are common in normal gestation, ectopic pregnancy, and molar pregnancy. Before initiating treatment, it is important to distinguish early pregnancy loss from other early pregnancy complications. Treatment of an early pregnancy loss before confirmed diagnosis can have detrimental consequences, including interruption of a normal pregnancy, pregnancy complications, or birth defects (9). Therefore, a thorough

Exhibit 2

evaluation is needed to make a definitive diagnosis. In combination with a thorough medical history and physical examination, ultrasonography and serum β-hCG testing can be helpful in making a highly certain diagnosis.

Ultrasonography, if available, is the preferred modality to verify the presence of a viable intrauterine gestation. In some instances, making a diagnosis of early pregnancy loss is fairly straightforward and requires limited testing or imaging. For example, early pregnancy loss can be diagnosed with certainty in a woman with an ultrasound-documented intrauterine pregnancy who subsequently presents with reported significant vaginal bleeding and an empty uterus on ultrasound examination. In other instances, the diagnosis of early pregnancy loss is not as clear. Depending on the specific clinical circumstances and how much diagnostic certainty the patient desires, a single serum β-hCG test or ultrasound examination may not be sufficient to confirm the diagnosis of early pregnancy loss.

The use of ultrasound criteria to confirm the diagnosis of early pregnancy loss was initially reported in the early 1990s, shortly after vaginal ultrasonography became widely available. Based on these early studies, a crown rump length (CRL) of 5 mm without cardiac activity or an empty gestational sac measuring 16 mm in mean gestational sac diameter have been used as diagnostic criteria to confirm early pregnancy loss (10, 11). Recently, two large prospective studies have been used to challenge these cutoffs. In the first study, 1,060 women with intrauterine pregnancies of uncertain viability were followed up to weeks 11 14 of gestation (12). In this group of women, 55.4% received a diagnosis of nonviable gestation during the observation period. A CRL cutoff of 5 mm was associated with an 8.3% false-positive rate for early pregnancy loss. A CRL cutoff of 5.3 mm was required to achieve a false-positive rate of 0% in this study (12). Similarly, the authors reported a 4.4% false-positive rate for early pregnancy loss when using a mean gestational sac diameter cutoff of 16 mm. A mean gestational sac diameter cutoff of 21 mm (without an embryo and with or without a yolk sac) on the first ultrasound examination was required to achieve 100% specificity for early pregnancy loss. In a second study of 359 women from the first study group, the authors concluded that growth rates for the gestational sac (mean gestational sac diameter) and the embryo (CRL) could not predict viability accurately (13). However, the authors concluded that if a gestational sac was empty on initial scan, the absence of a visible yolk sac or embryo on a second scan performed 7 days or more after the first scan was always associated with pregnancy loss (13).

Based on these studies, the Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy created guidelines that are considerably more conservative than past recommendations and also have stricter cutoffs than the studies on which they are based (14) (Table 1). The authors of the guidelines report that the stricter cutoffs are needed to account for interobserver variability; however, this already was accounted for in the original study through its use of multiple ultrasonographers (12, 15). Other important limitations in the development of these guidelines should be recognized. For example, there were few cases at or near the measurements ultimately identified as decision boundaries. Similarly, the time between observing a gestational sac and expecting to see a yolk sac or embryo was increased from 7 days or more in the clinical study (13) to 14 days in the guidelines (14). The basis of this recommendation is unclear.

Obstetrician gynecologists caring for women experiencing possible early pregnancy loss should consider other clinical factors when interpreting the Society of Radiologists in Ultrasound guidelines, including the woman's desire to continue the pregnancy; her willingness to postpone intervention to achieve 100% certainty of pregnancy loss; and the potential consequences of waiting for intervention, including unwanted spontaneous passage of pregnancy tissue, the need for an unscheduled visit or procedure, and patient anxiety. It is important to include the patient in the diagnostic process and to individualize these guidelines to patient circumstances.

Criteria that are considered suggestive, but not diagnostic, of early pregnancy loss are listed in Table 1 (14). Slow fetal heart rate (less than 100 beats per minute at 5 7 weeks of gestation) (16) and subchorionic hemorrhage also have been shown to be associated with early pregnancy loss but should not be used to make a definitive diagnosis (17). These findings warrant further evaluation in 7 10 days (14).

In cases in which an intrauterine gestation cannot be identified with reasonable certainty, serial serum β-hCG measurements and ultrasound examinations may be required before treatment to rule out the possibility of an ectopic pregnancy. A detailed description of the recommended approach to ectopic pregnancy diagnosis and management is available in Practice Bulletin Number 193, *Tubal Ectopic Pregnancy* (18).

▶ *What are the management options for early pregnancy loss?*

Accepted treatment options for early pregnancy loss include expectant management, medical treatment, or surgical evacuation. Although these options differ significantly in process, all have been shown to be reasonably effective and accepted by patients. In women without medical complications or symptoms requiring urgent surgical evacuation, treatment plans

Table 1. Guidelines for Transvaginal Ultrasonographic Diagnosis of Pregnancy Failure in a Woman With an Intrauterine Pregnancy of Uncertain Viability*

Findings Diagnostic of Pregnancy Failure	Findings Suspicious for, but Not Diagnostic of, Pregnancy Failure†
Crown–rump length of 7 mm or greater and no heartbeat	Crown–rump length of less than 7 mm and no heartbeat
Mean sac diameter of 25 mm or greater and no embryo	Mean sac diameter of 16–24 mm and no embryo
Absence of embryo with heartbeat 2 weeks or more after a scan that showed a gestational sac without a yolk sac	Absence of embryo with heartbeat 7–13 days after a scan that showed a gestational sac without a yolk sac
Absence of embryo with heartbeat 11 days or more after a scan that showed a gestational sac with a yolk sac	Absence of embryo with heartbeat 7–10 days after a scan that showed a gestational sac with a yolk sac
	Absence of embryo for 6 weeks or longer after last menstrual period
	Empty amnion (amnion seen adjacent to yolk sac, with no visible embryo)
	Enlarged yolk sac (greater than 7 mm)
	Small gestational sac in relation to the size of the embryo (less than 5 mm difference between mean sac diameter and crown–rump length)

*Criteria are from the Society of Radiologists in Ultrasound Multispecialty Consensus Conference on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy, October 2012.

†When there are findings suspicious for pregnancy failure, follow-up ultrasonography at 7–10 days to assess the pregnancy for viability is generally appropriate.

Reprinted from Doubilet PM, Benson CB, Bourne T, Blaivas M, Barnhart KT, Benacerraf BR, et al. Diagnostic criteria for nonviable pregnancy early in the first trimester. Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy. N Engl J Med 2013;369:1443–51.

can safely accommodate patient treatment preferences. There is no evidence that any approach results in different long-term outcomes. Patients should be counseled about the risks and benefits of each option. The following discussion applies to symptomatic and asymptomatic patients.

Expectant Management

Because of a lack of safety studies of expectant management in the second trimester and concerns about hemorrhage, expectant management generally should be limited to gestations within the first trimester. With adequate time (up to 8 weeks), expectant management is successful in achieving complete expulsion in approximately 80% of women (19). Limited data suggest that expectant management may be more effective in symptomatic women (those who report tissue passage or have ultrasound findings consistent with incomplete expulsion) than in asymptomatic women (20, 21). Furthermore, studies that included women with incomplete early pregnancy loss tend to report higher success rates than those that included only women with missed or anembryonic pregnancy loss (22).

Patients undergoing expectant management may experience moderate-to-heavy bleeding and cramping. Educational materials instructing the patient on when and who to call for excessive bleeding and prescriptions for pain medications should be provided. It also is important to counsel patients that surgery may be needed if complete expulsion is not achieved. Studies among women with early pregnancy loss typically have used ultrasound criteria, patient-reported symptoms, or both, to confirm complete passage of gestational tissue. Although there is no consensus in the literature, a commonly used criterion for complete expulsion of pregnancy tissue is the absence of a gestational sac and an endometrial thickness of less than 30 mm (23). However, there is no evidence that morbidity is increased in asymptomatic women with a thicker endometrial measurement (24). Surgical intervention is not required in asymptomatic women with a thickened endometrial stripe after treatment for early pregnancy loss. Thus, the use of ultrasound examination for any diagnostic purpose other than documenting the absence of the gestational sac is not recommended. Other follow-up approaches, such as standardized follow-up phone calls, urine pregnancy tests, or

serial quantitative serum β-hCG measurements, may be useful, especially for women with limited access to follow-up ultrasound examination (25). However, these approaches have not been studied sufficiently among women with early pregnancy loss to provide meaningful guidance.

Medical Management

Medical management for early pregnancy loss can be considered in women without infection, hemorrhage, severe anemia, or bleeding disorders who want to shorten the time to complete expulsion but prefer to avoid surgical evacuation. Compared with expectant management, medical management of early pregnancy loss decreases the time to expulsion and increases the rate of complete expulsion without the need for surgical intervention (26).

Misoprostol-based regimens have been extensively studied for the medical management of early pregnancy loss (26). Most studies suggest that a larger dose of misoprostol is more effective than a smaller dose, and vaginal or sublingual administration is more effective than oral administration, although the sublingual route is associated with more cases of diarrhea (26). The largest randomized controlled trial conducted in the United States demonstrated complete expulsion by day 3 in 71% of women with first-trimester pregnancy loss after one dose of 800 micrograms of vaginal misoprostol (23). The success rate was increased to 84% after a second dose of 800 micrograms of vaginal misoprostol was administered if needed. Therefore, in patients for whom medical management of early pregnancy loss is indicated, initial treatment using 800 micrograms of vaginal misoprostol is recommended, with a repeat dose as needed (Box 1).

The addition of a dose of mifepristone (200 mg orally) 24 hours before misoprostol administration may significantly improve treatment efficacy and should be considered when mifepristone is available (Box 1). Although initial studies were unclear about the benefit of mifepristone for the management of early pregnancy loss (27), a 2018 randomized controlled trial showed that a combined mifepristone misoprostol regimen was superior to misoprostol alone for the management of early pregnancy loss (28). Among 300 women undergoing medical management for early pregnancy loss, those who received mifepristone (200 mg orally) followed by misoprostol (800 micrograms vaginally) 24 hours later had significantly increased rates of complete expulsion (relative risk [RR], 1.25; 95% CI, 1.09 1.43) compared with women who received misoprostol alone (800 micrograms vaginally) (28). The mifepristone misoprostol regimen also was associated with a decreased risk of surgical intervention with uterine aspiration to complete treatment (RR, 0.37; 95% CI, 0.21 0.68). Reports of bleeding intensity and pain as well as other adverse effects were generally similar for the two treatment groups, and the occurrence of serious adverse events was rare among all participants. These results are consistent with the demonstrated efficacy and safety of the mifepristone misoprostol combined regimen for medication-induced abortion (29, 30). Currently, the availability of mifepristone is limited by U.S. Food and Drug Administration Risk Evaluation and Mitigation Strategy restrictions (31). The American College of Obstetricians and Gynecologists supports improving access to mifepristone for reproductive health indications (32).

A 2013 Cochrane review of limited evidence concluded that among women with incomplete pregnancy loss (ie, incomplete tissue passage), the addition of

Box 1. Protocol for the Medical Management of Early Pregnancy Loss

- Misoprostol 800 micrograms vaginally, with one repeat dose as needed, no earlier than 3 hours after the first dose and typically within 7 days if there is no response to the first dose*
- A dose of mifepristone (200 mg orally) 24 hours before misoprostol administration should be considered when mifepristone is available.†
- Prescriptions for pain medications should be provided to the patient.
- Women who are Rh(D) negative and unsensitized should receive Rh(D)-immune globulin within 72 hours of the first misoprostol administration.
- Follow-up to document the complete passage of tissue can be accomplished by ultrasound examination, typically within 7–14 days. Serial serum β-hCG measurements may be used instead in settings where ultrasonography is unavailable. Patient-reported symptoms also should be considered when determining whether complete expulsion has occurred.
- If medical management fails, the patient may opt for expectant management, for a time determined by the woman and her obstetrician–gynecologist or other gynecologic provider, or suction curettage.

*Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. N Engl J Med 2005;353:761–9.

†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.

misoprostol does not clearly result in higher rates of complete evacuation when compared with expectant management (at 7 10 days, success rates were 80 81% versus 52 85%, respectively) (33). Therefore, at this time, there is insufficient evidence to support or refute the use of misoprostol among women with incomplete pregnancy loss.

As with expectant management of early pregnancy loss, women opting for medical treatment should be counseled on what to expect while they pass pregnancy tissue, provided information on when to call regarding bleeding, and given prescriptions for pain medications. Counseling should emphasize that the woman is likely to have bleeding that is heavier than menses (and potentially accompanied by severe cramping). The woman should understand how much bleeding is considered too much. An easy reference for the patient to use is the soaking of two maxi pads per hour for 2 consecutive hours (34). The patient should be advised to call her obstetrician gynecologist or other gynecologic provider if she experiences this level of bleeding. As with expectant management, it also is important to counsel patients that surgery may be needed if medical management does not achieve complete expulsion.

Follow-up typically includes confirmation of complete expulsion by ultrasound examination, but serial serum β-hCG measurement may be used instead in settings where ultrasonography is unavailable. Patient-reported symptoms also should be considered when determining whether complete expulsion has occurred.

Surgical Management

Surgical uterine evacuation has long been the traditional approach for women presenting with early pregnancy loss and retained tissue. Women who present with hemorrhage, hemodynamic instability, or signs of infection should be treated urgently with surgical uterine evacuation. Surgical evacuation also might be preferable in other situations, including the presence of medical comorbidities such as severe anemia, bleeding disorders, or cardiovascular disease. Many women prefer surgical evacuation to expectant or medical treatment because it provides more immediate completion of the process with less follow-up.

In the past, uterine evacuation often was performed with sharp curettage alone. However, studies show that the use of suction curettage is superior to the use of sharp curettage alone (35, 36). Furthermore, the routine use of sharp curettage along with suction curettage in the first trimester does not provide any additional benefit as long as the obstetrician gynecologist or other gynecologic provider is confident that the uterus is empty. Suction curettage also can be performed in an office setting with an electric vacuum source or manual vacuum aspirator, under local anesthesia with or without the addition of sedation (37, 38). Surgical management in the office setting offers significant cost savings compared with the same procedure performed in the operating room (38 40). Patients often choose management in the office setting for its convenience and scheduling availability (38).

▶ *How do the different management options for early pregnancy loss compare in effectiveness and risk of complications?*

Studies have demonstrated that expectant, medical, and surgical management of early pregnancy loss all result in complete evacuation of pregnancy tissue in most patients, and serious complications are rare. As a primary approach, surgical evacuation results in faster and more predictable complete evacuation (22). The success of surgical uterine evacuation of early pregnancy loss approaches 99% (23). The largest U.S. trial reported that success rates after medical management of anembryonic gestations (81%) was lower than with embryonic or fetal death (88%) or incomplete or inevitable early pregnancy loss (93%) (23). However, a subsequent multivariable analysis of the same data revealed that only active bleeding and nulliparity were strong predictors of success (41). Therefore, medical management is a reasonable option for any pregnancy failure type.

Overall, serious complications after early pregnancy loss treatment are rare and are comparable across treatment types. Clinically important intrauterine adhesion formation is a rare complication after surgical evacuation. Hemorrhage and infection can occur with all of the treatment approaches. In the Management of Early Pregnancy Failure Trial, women randomized to the misoprostol group were significantly more likely to have a decrease in their hemoglobin levels greater than or equal to 3 g/dL than women in the vacuum aspiration group (23, 42). However, rates of hemorrhage-related hospitalization with or without transfusion are similar between treatment approaches (0.5 1%) (23, 43). Pelvic infection also can occur after any type of early pregnancy loss treatment. One systematic review concluded that although infection rates appeared lower among those undergoing expectant management than among those undergoing surgical evacuation (RR, 0.29; 95% CI, 0.09 0.97), the overall rates of infection were low (1 2%) (43). Because neither approach was clearly superior, the reviewers concluded that patient preference should guide choice of intervention (43).

The risk of infection after suction curettage for missed early pregnancy loss should be similar to that after suction curettage for induced abortion. Therefore, despite the lack of data, antibiotic prophylaxis also should be considered for patients with early pregnancy loss (44, 45). The use of a single preoperative dose of doxycycline is recommended to prevent infection after surgical management of early pregnancy loss. Some experts have recommended administration of a single 200-mg dose of doxycycline 1 hour before surgical management of early pregnancy loss to prevent postoperative infection. The use of antibiotics based only on the diagnosis of incomplete early pregnancy loss has not been found to reduce infectious complications as long as unsafe induced abortion is not suspected (46). The benefit of antibiotic prophylaxis for the medical management of early pregnancy loss is unknown.

▶ *How do the different treatment approaches to early pregnancy loss differ with respect to cost?*

Studies have consistently shown that surgical management in an operating room is more costly than expectant or medical management (47, 48). However, surgical management in an office setting can be more effective and less costly than medical management when performed without general anesthesia and in circumstances in which numerous office visits are likely or there is a low chance of success with medical management or expectant management (49). Findings from studies comparing the cost-effectiveness of medical and expectant management schemes are inconsistent. However, a U.S. analysis of all three management approaches concluded that medical management with misoprostol was the most cost-effective intervention (48). One limitation of the available studies on cost of early pregnancy loss care is that none of these studies can adequately consider clinical nuances or patient treatment preferences, which can affect patient adherence to the primary treatment regimen and, subsequently, the effectiveness of that treatment. For instance, in one observational study, the effectiveness of medical management of early pregnancy loss was far lower than rates reported in randomized clinical trials, which was due in large part to patients' unwillingness to complete the treatment regimen (50).

▶ *How should patients be counseled regarding interpregnancy interval after early pregnancy loss?*

There are no quality data to support delaying conception after early pregnancy loss to prevent subsequent early pregnancy loss or other pregnancy complications. Small observational studies show no benefit to delayed conception after early pregnancy loss (51, 52). Abstaining from vaginal intercourse for 1 2 weeks after complete passage of pregnancy tissue generally is recommended to reduce the risk of infection, but this is not an evidence-based recommendation.

▶ *How should patients be counseled regarding the use of contraception after early pregnancy loss?*

Women who desire contraception may initiate hormonal contraception use immediately after completion of early pregnancy loss (53). There are no contraindications to the placement of an intrauterine device immediately after surgical treatment of early pregnancy loss as long as septic abortion is not suspected (53). The expulsion rate with immediate intrauterine device insertion after suction curettage in the first trimester is not clinically significantly different than placement 2 6 weeks postoperatively (5% versus 2.7% at 6 months) (54).

▶ *How should patients be counseled regarding prevention of alloimmunization after early pregnancy loss?*

Although the risk of alloimmunization is low, the consequences can be significant, and administration of Rh D immune globulin should be considered in cases of early pregnancy loss, especially those that are later in the first trimester. If given, a dose of at least 50 micrograms should be administered. Because of the higher risk of alloimmunization, Rh D-negative women who have surgical management of early pregnancy loss should receive Rh D immune globulin prophylaxis (55).

▶ *What type of workup is needed after early pregnancy loss?*

No workup generally is recommended until after the second consecutive clinical early pregnancy loss (7). Maternal or fetal chromosomal analyses or testing for inherited thrombophilias are not recommended routinely after one early pregnancy loss. Although thrombophilias commonly are thought of as causes of early pregnancy loss, only antiphospholipid syndrome consistently has been shown to be significantly associated with early pregnancy loss (56, 57). In addition, the use of anticoagulants, aspirin, or both, has not been shown to reduce the risk of early pregnancy loss in women with thrombophilias except in women with antiphospholipid syndrome (58, 59).

▶ ***Are there any effective interventions to prevent early pregnancy loss?***

There are no effective interventions to prevent early pregnancy loss. Therapies that have historically been recommended, such as pelvic rest, vitamins, uterine relaxants, and administration of β-hCG, have not been proved to prevent early pregnancy loss (60 62). Likewise, bed rest should not be recommended for the prevention of early pregnancy loss (63). A 2008 Cochrane review found no effect of prophylactic progesterone administration (oral, intramuscular, or vaginal) in the prevention of early pregnancy loss (64). For threatened early pregnancy loss, the use of progestins is controversial, and conclusive evidence supporting their use is lacking (65). Women who have experienced at least three prior pregnancy losses, however, may benefit from progesterone therapy in the first trimester (7).

Summary of Recommendations and Conclusions

The following recommendation and conclusion are based on good and consistent scientific evidence (Level A):

- In patients for whom medical management of early pregnancy loss is indicated, initial treatment using 800 micrograms of vaginal misoprostol is recommended, with a repeat dose as needed. The addition of a dose of mifepristone (200 mg orally) 24 hours before misoprostol administration may significantly improve treatment efficacy and should be considered when mifepristone is available.
- The use of anticoagulants, aspirin, or both, has not been shown to reduce the risk of early pregnancy loss in women with thrombophilias except in women with antiphospholipid syndrome.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Ultrasonography, if available, is the preferred modality to verify the presence of a viable intrauterine gestation.
- Surgical intervention is not required in asymptomatic women with a thickened endometrial stripe after treatment for early pregnancy loss.
- The routine use of sharp curettage along with suction curettage in the first trimester does not provide any additional benefit as long as the obstetrician gynecologist or other gynecologic provider is confident that the uterus is empty.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Accepted treatment options for early pregnancy loss include expectant management, medical treatment, or surgical evacuation. In women without medical complications or symptoms requiring urgent surgical evacuation, treatment plans can safely accommodate patient treatment preferences.
- The use of a single preoperative dose of doxycycline is recommended to prevent infection after surgical management of early pregnancy loss.
- Although the risk of alloimmunization is low, the consequences can be significant, and administration of Rh D immune globulin should be considered in cases of early pregnancy loss, especially those that are later in the first trimester.
- Because of the higher risk of alloimmunization, Rh D-negative women who have surgical management of early pregnancy loss should receive Rh D immune globulin prophylaxis.

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65. Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA. Progestogen for treating threatened miscarriage. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD005943. DOI: 10.1002/14651858.CD005943.pub4. (Meta analysis)

The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 July 2014. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly de signed randomized controlled trial.

II 1 Evidence obtained from well designed controlled trials without randomization.

II 2 Evidence obtained from well designed cohort or case control analytic studies, preferably from more than one center or research group.

II 3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A Recommendations are based on good and consistent scientific evidence.

Level B Recommendations are based on limited or inconsistent scientific evidence.

Level C Recommendations are based primarily on consensus and expert opinion.

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Exhibit 3

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Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss

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ABSTRACT

BACKGROUND

Medical management of early pregnancy loss is an alternative to uterine aspiration, but standard medical treatment with misoprostol commonly results in treatment failure. We compared the efficacy and safety of pretreatment with mifepristone followed by treatment with misoprostol with the efficacy and safety of misoprostol use alone for the management of early pregnancy loss.

METHODS

We randomly assigned 300 women who had an anembryonic gestation or in whom embryonic or fetal death was confirmed to receive pretreatment with 200 mg of mifepristone, administered orally, followed by 800 μg of misoprostol, administered vaginally (mifepristone-pretreatment group), or 800 μg of misoprostol alone, administered vaginally (misoprostol-alone group). Participants returned 1 to 4 days after misoprostol use for evaluation, including ultrasound examination, by an investigator who was unaware of the treatment-group assignments. Women in whom the gestational sac was not expelled were offered expectant management, a second dose of misoprostol, or uterine aspiration. We followed all participants for 30 days after randomization. Our primary outcome was gestational sac expulsion with one dose of misoprostol by the first follow-up visit and no additional intervention within 30 days after treatment.

RESULTS

Complete expulsion after one dose of misoprostol occurred in 124 of 148 women (83.8%; 95% confidence interval [CI], 76.8 to 89.3) in the mifepristone-pretreatment group and in 100 of 149 women (67.1%; 95% CI, 59.0 to 74.6) in the misoprostol-alone group (relative risk, 1.25; 95% CI, 1.09 to 1.43). Uterine aspiration was performed less frequently in the mifepristone-pretreatment group than in the misoprostol-alone group (8.8% vs. 23.5%; relative risk, 0.37; 95% CI, 0.21 to 0.68). Bleeding that resulted in blood transfusion occurred in 2.0% of the women in the mifepristone-pretreatment group and in 0.7% of the women in the misoprostol-alone group (P=0.31); pelvic infection was diagnosed in 1.3% of the women in each group.

CONCLUSIONS

Pretreatment with mifepristone followed by treatment with misoprostol resulted in a higher likelihood of successful management of first-trimester pregnancy loss than treatment with misoprostol alone. (Funded by the National Institute of Child Health and Human Development; PreFaiR ClinicalTrials.gov number, NCT02012491.)

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Exhibit 3

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A Quick Take is available at NEJM.org

First-trimester miscarriage, or early pregnancy loss, is the most common complication in pregnancy and affects approximately 1 million women in the United States annually.[1,2] Subtypes of early pregnancy loss include anembryonic gestation and embryonic or fetal death, inevitable abortion, and incomplete abortion.[3,4] Before the advent of home pregnancy testing and early ultrasonography, women often presented with heavy bleeding or signs of infection requiring prompt treatment with dilation and curettage.[5] Currently, women frequently receive a diagnosis of early pregnancy loss before the onset of symptoms. This decrease in exigent presentations has led to an interest in pursuing nonsurgical treatment options for pregnancy loss.[6,7] Although some women pursue expectant management, women generally prefer active management[6,8-12]; the ability to have control over the management of miscarriage may relieve some of the emotional burden that accompanies first-trimester pregnancy loss.[12-14]

Medical management of early pregnancy loss with prostaglandin analogues allows for planned, expedited expulsion of the nonviable pregnancy tissue, with the goal of avoiding a surgical procedure. Misoprostol is stable at room temperature and can be administered by the woman herself, which allows the tissue expulsion to occur in the privacy of a woman's home at a time she chooses.[15] Medical management is highly desired by many women, and the use of misoprostol is recommended by society guidelines in the United States and throughout the world.[16,17] Unfortunately, the standard dose of 800 μg of misoprostol, administered vaginally, has low efficacy among women with a closed cervical os. As many as 15 to 40% of such women require a second dose of misoprostol, which prolongs the treatment period, or ultimately require the uterine evacuation procedure they wished to avoid.[3,7-9,18] The rate of failure diminishes the clinical usefulness of this strategy in practice.[12]

Mifepristone is a 19-nor steroid that acts as a competitive progesterone-receptor antagonist and a glucocorticoid-receptor antagonist and primes the myometrium and cervix for prostaglandin activity.[15,19,20] The reported effectiveness of combination treatment with mifepristone and misoprostol for early pregnancy loss has ranged from 52 to 95%.[3,10,11,21,22] This wide range is due in part to heterogeneity in study designs and outcome definitions.[3] To date, the usefulness of mifepristone in the treatment of early pregnancy loss has remained unclear. We performed a randomized trial to compare the efficacy and safety of pretreatment with mifepristone followed by treatment with misoprostol with misoprostol use alone for the management of anembryonic gestation and embryonic or fetal death in women in clinically stable condition who have a closed cervical os.

METHODS

TRIAL DESIGN

From May 2014 through April 2017, women who received a diagnosis of anembryonic gestation or embryonic or fetal death were referred to the study team for screening; an investigator confirmed eligibility before enrollment. All participants provided written informed consent. The Comparative Effectiveness of Pregnancy Failure Management Regimens (PreFaiR) trial was approved by the institutional review boards at the University of Pennsylvania, the University of California, Davis, and the Albert Einstein College of Medicine. All the authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol. Mifepristone (Mifeprex) was purchased from the manufacturer (Danco Laboratories) at a research price for use in the trial and was dispensed at the trial sites; the manufacturer had no other role in the trial. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

PARTICIPANTS

Healthy women 18 years of age or older were eligible if they had an ultrasound examination that showed a nonviable intrauterine pregnancy between 5 and 12 completed weeks of gestation. We excluded women who had an incomplete or inevitable abortion (defined as the absence of a gestational sac, an open cervical os, or both) because of the high efficacy of misoprostol use alone in women with these diagnoses.[4] Women were also excluded if they had a contraindication to mifepristone or misoprostol, had any evidence of a viable or ectopic pregnancy, had a hemoglobin level lower than 9.5 g per deciliter, had a

known clotting defect or were receiving anticoagulants, had a pregnancy with an intrauterine device in place, or were unwilling to adhere to the trial protocol.

TRIAL PROCEDURES

We randomly assigned the participants to receive pretreatment with 200 mg of mifepristone, administered orally, followed by 800 μg of misoprostol, administered vaginally approximately 24 hours later (mifepristone-pretreatment group), or standard therapy with 800 μg of misoprostol alone, administered vaginally (misoprostol-alone group), on trial day 1. Participants were randomly assigned in permuted blocks of two to eight, stratified according to trial site, with the use of Research Electronic Data Capture software (REDCap, Vanderbilt University). Women who were assigned to the mifepristone-pretreatment group swallowed the mifepristone in front of one of the trial staff members. In accordance with our pragmatic trial design, the women in the misoprostol-alone group did not receive placebo.[23] We instructed all participants in both treatment groups to insert four misoprostol tablets (200 μg per tablet) vaginally at home approximately 24 hours after randomization. We offered women oral analgesics according to the local standards at each trial site. Trial staff provided each participant a diary to record information about bleeding, symptoms, and pain medication use. Participants were scheduled for an initial follow-up appointment at least 24 hours (but not more than 4 days) after misoprostol use (trial day 3).

At the initial follow-up visit, an investigator who was unaware of the treatment-group assignments assessed the outcome by means of endovaginal ultrasonography. If the gestational sac was absent, a follow-up telephone call was scheduled approximately 1 week after randomization. If the gestational sac was present, we offered women a second dose of misoprostol or expectant or surgical management. Participants who chose expectant management or a second dose of misoprostol returned for an additional follow-up visit approximately 8 days (range, 6 to 12) after randomization for evaluation by an investigator who was unaware of the treatment-group assignments. We contacted all participants by telephone 30 days (range, 25 to 36) after randomization to collect information about additional treatments or adverse events. At this time, participants assessed bleeding and pain (on Likert scales, on which scores ranged from 1 to 5, with lower scores indicating greater bleeding and pain) and responded to standard questions regarding the acceptability of treatment.[8,24,25]

OUTCOMES AND ADVERSE EVENTS

The primary outcome was gestational sac expulsion by the first follow-up visit with one dose of misoprostol and no additional surgical or medical intervention within 30 days after treatment; the attainment of the primary outcome was classified as treatment success. We chose this primary outcome in accordance with patient preferences for the treatment to work promptly and effectively. We also planned assessments of the treatment outcomes at the day 8 and day 30 time points according to three commonly used clinical metrics: the rate of gestational sac expulsion with one dose of misoprostol, the rate of gestational sac expulsion with two doses of misoprostol, and the percentage of women who underwent uterine aspiration. Additional prespecified secondary outcomes (for which results are presented in the current report) included adverse effects (including bleeding and pain, as measured on Likert scales), acceptability of treatment (an overall assessment of the treatment, as measured on a 3-point scale [with "good" indicating a positive experience, "bad" a negative experience, or neutral] and with the question, "Would you recommend this method of treatment to a friend?"), and assessment of clinical characteristics associated with complete gestational sac expulsion; assessments of quality of life, costs, and biomarkers that predict complete gestational sac expulsion were performed, but the data are not presented here.

STATISTICAL ANALYSIS

On the basis of previous research, we expected the rate of treatment success with a single dose of misoprostol to be 80 to 90% in the mifepristone-pretreatment group and 60 to 71% in the misoprostol-alone group.[8,10,18] We estimated that a sample size of 134 participants per treatment group would provide adequate power to detect a 15 percentage-point difference in the rate of treatment success (85% in the mifepristone-

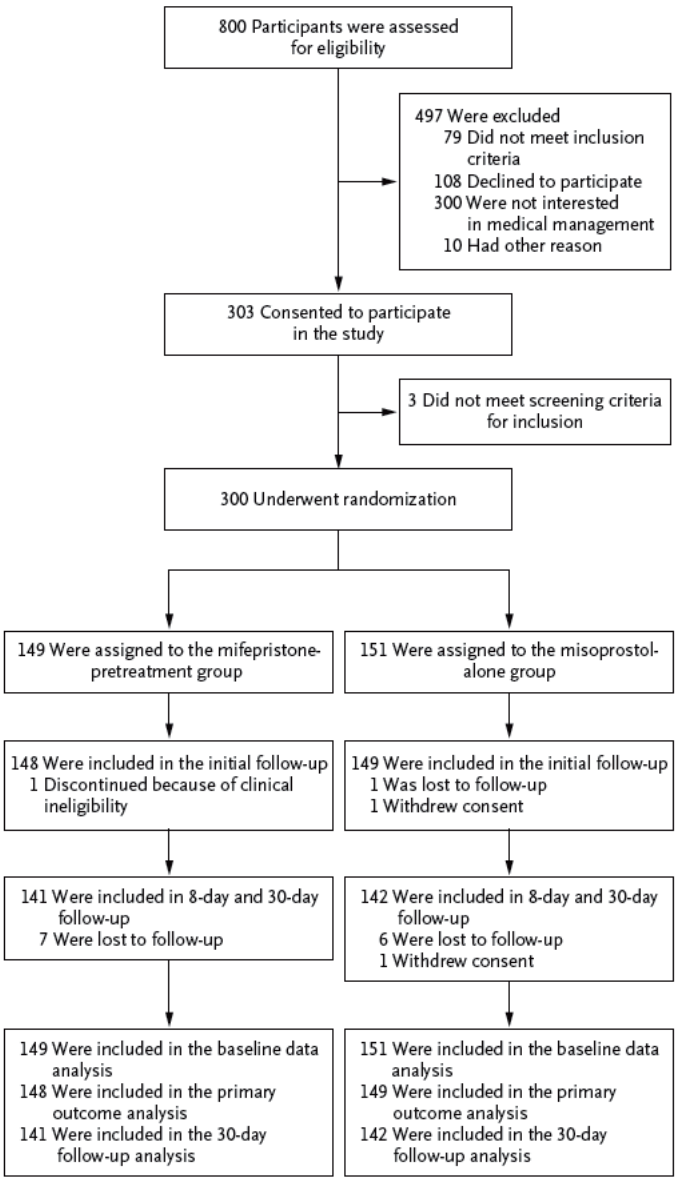

Figure 1. Enrollment, Randomization, Follow-up, and Analysis.

Participants assigned to the mifepristone-pretreatment group received 200 mg of mifepristone, administered orally, followed by 800 μg of misoprostol, administered vaginally approximately 24 hours later, and those assigned to the misoprostol-alone group received 800 μg of misoprostol alone, administered vaginally. All participants received the assigned treatment.

pretreatment group vs. 70% in the misoprostol-alone group). Allowing for a single interim analysis under a group sequential design and a loss to follow-up of 5%, we set an overall recruitment goal of 300 women. Data analysis were performed with Stata software, version 15 (StataCorp). Standard descriptive methods were used to summarize the trial population overall and by treatment group. The primary outcome was assessed among all women who had at least one follow-up visit according to a preplanned modified intention-to-treat principle. After testing for homogeneity of the primary outcome among trial sites, we calculated the percentage (with 95% confidence interval) of women in each treatment group who had treatment success and compared the results using two-sided Mantel–Haenszel combined relative risks at an alpha level of 0.047 (an alpha level of 0.003 was allocated to the interim analysis). We computed the effect of loss to follow-up by performing a sensitivity analysis in which the outcome that was most in favor of no treatment effect (i.e., failure in the mifepristone-pretreatment group and success in the misoprostol-alone group) was assigned to each participant who was lost to follow-up.

Subgroup analyses of the primary outcome according to patient demographics and clinical characteristics were prespecified; we performed analyses that were stratified according to gestational age, parity, gravidity, and diagnosis (embryonic or fetal death vs. anembryonic gestation). (The protocol also specified an analysis according to presenting symptoms, but this was not performed owing to the low percentage of participants who presented with bleeding.) Two-sided Mantel–Haenszel combined relative risks were used to compare treatment groups in all secondary analyses; the results are presented without adjustment for multiplicity and should be considered exploratory. In accordance with the protocol, the data and safety monitoring committee performed one interim analysis for safety and futility after recruitment of half the participants; on the basis of the findings from this interim analysis, the trial was continued.

RESULTS

PARTICIPANTS

From May 2014 through April 2017, we assessed 800 women for eligibility; 497 women were excluded and 303 consented to participate (Fig. 1). The most common reason for declining participation was a preference for uterine aspiration

over medical management. Of the 303 women enrolled, 3 did not meet screening criteria for inclusion; thus, 300 women underwent randomization, with 149 assigned to the mifepristone-pretreatment group and 151 assigned to the misoprostol-alone group. All the participants completed the trial according to the protocol with the exception of 2 women who were lost to follow-up and 1 woman who was determined to be clinically ineligible after randomization because of suspicion of a cesarean-section-scar ectopic pregnancy (an ectopic pregnancy implanted in scar tissue from a previous cesarean section). Baseline characteristics were similar in the two treatment groups (Table 1).

OUTCOMES

Initial Follow-up

The median number of days between the time of misoprostol administration and the first follow-up visit was 2.0 (range, 0.5 to 5.5) in the mifepristone-pretreatment group and 2.6 (range, 0.7 to 9.6) in the misoprostol-alone group (P=0.04). Treatment success by the first follow-up visit, with no additional interventions needed within 30 days after treatment, occurred in 124 of 148 women (83.8%; 95% confidence interval [CI], 76.8 to 89.3) in the mifepristone-pretreatment group and in 100 of 149 women (67.1%; 95% CI, 59.0 to 74.6) in the misoprostol-alone group (absolute difference in the rate of treatment success, 16.7 percentage points [95% CI, 7.1 to 26.3]; relative risk of expulsion with one dose of misoprostol, 1.25 [95% CI, 1.09 to 1.43]) (Table 2). The results were similar in a sensitivity analysis that assumed that the outcomes in the women who were lost to follow-up were most in favor of no treatment effect (i.e., treatment failure with mifepristone pretreatment and treatment success with misoprostol alone) (relative risk, 1.21; 95% CI, 1.05 to 1.38). In the mifepristone-pretreatment group, 65 women (43.6%) did not wait the full 24 hours before administering misoprostol (mean [±SD] number of hours waited, 12.0±7.3), of whom 45 (69.2%) waited for less than 18 hours. The rate of treatment success among women who did not wait the full 24 hours before administering misoprostol was 79.7%, as compared with 86.9% among the women who waited for 24 hours (P=0.24). The number needed to pretreat with mifepristone to attain an additional outcome of treatment success by the first follow-up visit was 6.

Day 8 Follow-up

Gestational sac expulsion did not occur by the first follow-up visit in 24 women in the mifepristone-pretreatment group (16.2%) and in 49 women in the misoprostol-alone group (32.9%); among these women, 41% chose expectant management, 27% chose a second dose of misoprostol, and 31% underwent uterine aspiration (Table S1 in the Supplementary Appendix, available at NEJM.org). Among the women who did not have treatment success by the first follow-up visit, there were no significant between-group differences in the proportion of women who chose each additional intervention (P=0.12). Complete expulsion of the gestational sac with one dose of misoprostol by day 8 occurred in 130 of 148 women (87.8%; 95% CI, 81.5 to 92.6) in mifepristone-pretreatment group and in 106 of 149 women (71.1%; 95% CI, 63.2 to 78.3) in the misoprostol-alone group (relative risk, 1.23; 95% CI, 1.10 to 1.39).

Day 30 Follow-up

One month after randomization, the cumulative rate of gestational sac expulsion with up to two doses of misoprostol was 91.2% (95% CI, 85.4 to 95.2) in the mifepristone-pretreatment group and 75.8% (95% CI, 68.2 to 82.5) in the misoprostol-alone group. By the end of the trial period at day 30, a total of 13 women (8.8%; 95% CI, 4.8 to 14.6) in the mifepristone-pretreatment group and 35 women (23.5%; 95% CI, 16.9 to 31.1) in the misoprostol-alone group had undergone uterine aspiration (absolute difference, 14.7 percentage points [95% CI, 6.5 to 22.9]; relative risk, 0.37 [95% CI, 0.21 to 0.68]) (Table 2).

We performed subgroup analyses stratified according to length of gestation, parity, gravidity, and diagnosis (embryonic or fetal death vs. anembryonic gestation). Rates of treatment success by the first follow-up visit among women who were at 9 weeks of gestation or less were 84.8% (117 of 138 women) in the mifepristone-pretreatment group and 66.7% (94 of 141 women) in the misoprostol-alone group. No significant between-group differences were found in the effect of the intervention according to subgroups stratified by gestation, gravidity, parity, or diagnosis (Fig. 2).

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Mifepristone-Pretreatment Group (N=149)	Misoprostol-Alone Group (N=151)
Age — yr	30.7±6.3	30.2±6.0
Race or ethnic group — no. (%)†		
Black	65 (43.6)	67 (44.4)
White	57 (38.3)	52 (34.4)
Hispanic	38 (25.5)	38 (25.5)
Asian	9 (6.0)	11 (7.3)
Other	18 (12.1)	21 (13.9)
Education‡		
Some grade school or high school	10 (6.8)	17 (11.3)
High-school diploma or GED	46 (31.1)	56 (37.1)
Some college or post–high-school education	92 (62.2)	78 (51.7)
Medical insurance‡		
None	13 (8.8)	11 (7.3)
Medicaid or Medicare	64 (43.2)	78 (51.7)
Private insurance	71 (48.0)	62 (41.1)
Gravidity		
1	37 (24.8)	32 (21.2)
2	36 (24.2)	27 (17.9)
≥3	76 (51.0)	92 (60.9)
Parity		
0	63 (42.3)	52 (34.4)
≥1	86 (57.7)	99 (65.6)
Living children	87 (58.4)	94 (62.3)
Previous miscarriage	53 (35.6)	52 (34.4)
Gestation		
4–5 wk	15 (10.1)	10 (6.6)
6 wk	44 (29.5)	38 (25.2)
7 wk	34 (22.8)	46 (30.5)
8 wk	31 (20.8)	34 (22.5)
9 wk	14 (9.4)	15 (9.9)
10–12 wk	11 (7.4)	8 (5.3)
Diagnosis		
Anembryonic gestation	40 (26.8)	37 (24.5)
Embryonic or fetal death	109 (73.2)	114 (75.5)
Any bleeding before randomization		
Yes	18 (12.1)	17 (11.3)
No	111 (74.5)	119 (78.8)
Unknown	20 (13.4)	15 (9.9)

* Plus–minus values are means ±SD. Participants assigned to the mifepristone-pretreatment group received 200 mg of mifepristone, administered orally, followed by 800 μg of misoprostol, administered vaginally approximately 24 hours later, and those assigned to the misoprostol-alone group received 800 μg of misoprostol alone, administered vaginally. There were no significant differences between the groups in any of the characteristics listed. Percentages may not sum to 100 because of rounding.
† Race and ethnic group were reported by the participants; participants could report both race and Hispanic ethnicity.
‡ One participant in the mifepristone-pretreatment group was excluded because of missing values.

Table 2. Clinical Outcomes among Women Who Received Medical Treatment for Early Pregnancy Loss.

Outcome	Mifepristone-Pretreatment Group (N = 148)	Misoprostol-Alone Group (N = 149)	Relative Risk (95% CI)*
	number (percent)		
Gestational sac expulsion by the first follow-up visit: treatment success†	124 (83.8)	100 (67.1)	1.25 (1.09–1.43)‡
Gestational sac expulsion by the second follow-up visit at day 8	132 (89.2)	111 (74.5)	1.20 (1.07–1.33)
With 1 dose of misoprostol	130 (87.8)	106 (71.1)	
With 2 doses of misoprostol	2 (1.4)	5 (3.4)	
Gestational sac expulsion by the 30-day telephone call	135 (91.2)	113 (75.8)	1.20 (1.08–1.33)
With 1 dose of misoprostol	130 (87.8)	106 (71.1)	
With 2 doses of misoprostol	5 (3.4)	7 (4.7)	
Uterine aspiration§	13 (8.8)	35 (23.5)	0.37 (0.21–0.68)

* Relative risks were adjusted for trial site with use of the Mantel–Haenszel method.
† Treatment success was defined as gestational sac expulsion with one misoprostol dose by the first follow-up visit and no additional intervention within 30 days after treatment.
‡ The rate of treatment success by the first follow-up visit was significantly higher in the mifepristone-pretreatment group than in misoprostol-alone group (P<0.001).
§ Indications for uterine aspiration included participant request and clinical recommendation.

SIDE EFFECTS AND ACCEPTABILITY OF TREATMENT

The rates of serious adverse events and adverse events by type are provided in Table 3. There were no significant between-group differences in the mean scores for bleeding intensity (1.8 in both groups) or pain (2.7 in both groups). By the end of the trial period, 89.4% of the women in the mifepristone-pretreatment group and 87.4% in the misoprostol-alone group described their experience overall as either "good" or "neutral"; the corresponding percentages of women who stated that they would recommend their treatment method to a friend were 87.0% and 89.6%. The majority of women in each group (69.1% in the mifepristone-pretreatment group and 64.8% the misoprostol-alone group) also stated that they would use medical management if they had another pregnancy loss.

DISCUSSION

In this randomized trial involving women with anembryonic gestation or in whom embryonic or fetal death was confirmed, pretreatment with mifepristone followed by treatment with misoprostol resulted in a significantly higher rate of complete gestational sac expulsion by approximately 2 days after treatment than misoprostol use alone. Pretreatment with mifepristone also resulted in a significantly lower rate of uterine aspiration than misoprostol use alone.

Even in the context of our pragmatic trial design in which women received routine clinical care after the first follow-up visit, we had high rates of participant retention and adherence to the protocol. Our trial population was diverse with respect to sociodemographic status and pregnancy diagnosis, which supports the generalizability of the results. We did not include a placebo group in this pragmatic trial. Because the primary outcome was not reported by the participants but was assessed by an investigator who was unaware of the treatment-group assignments, we do not expect that the lack of a placebo group introduced bias related to the primary outcome. It is possible that secondary efficacy outcomes could have been affected, because women in the misoprostol-alone group who did not have gestational sac expulsion by the first follow-up visit might have been less willing to wait (i.e., to choose expectant management) until day 8 for tissue expulsion than those in the mifepristone-pretreatment group, but we did not find that the proportion of additional interventions differed significantly between the treatment groups. We allowed for a short range of days at

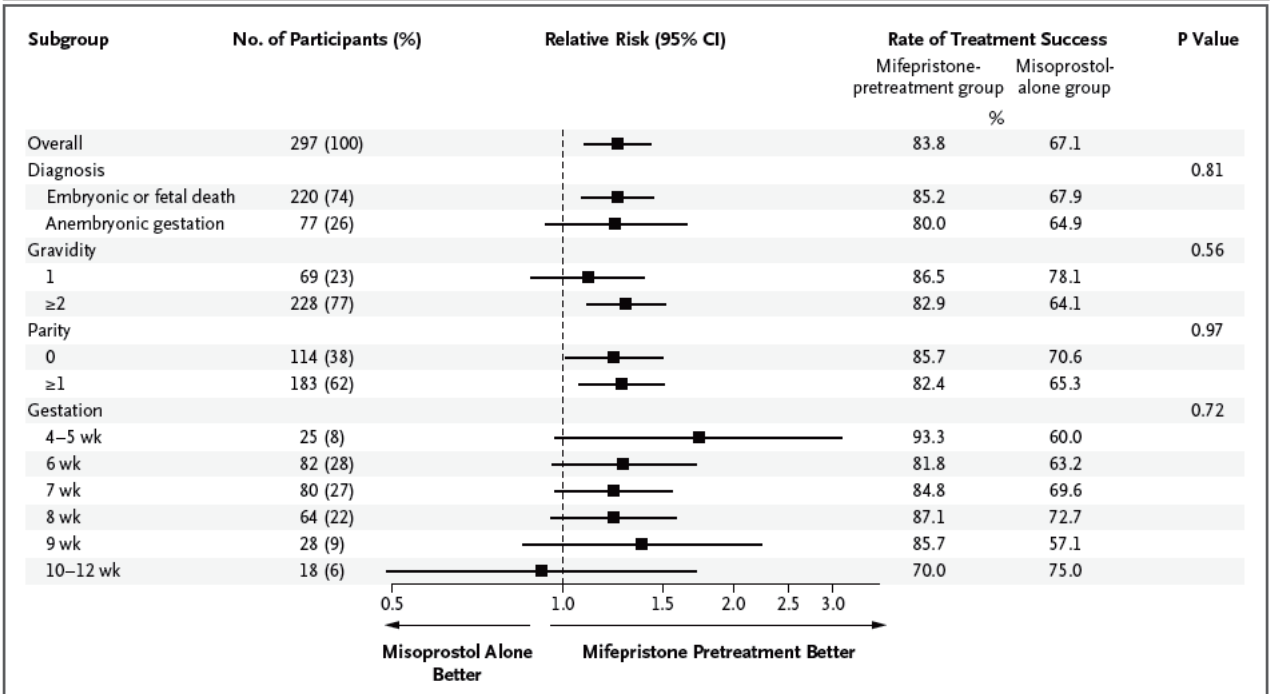

Figure 2. Clinical Outcomes among Women Who Received Medical Treatment for Early Pregnancy Loss, Stratified According to Clinical Characteristics.

Treatment success was defined as gestational sac expulsion with one dose of misoprostol by the first follow-up visit and no additional intervention within 30 days after treatment. P values were calculated from tests of interaction between the treatment groups and the subgroup variables.

which we initially assessed the primary outcome to accommodate the scheduling preferences of the participants. The slightly longer mean elapsed time between misoprostol use and follow-up assessment in the misoprostol-alone group would have biased against the benefit of pretreatment, even though a significant benefit of pretreatment was found.

We evaluated the 800-μg dose of misoprostol, administered vaginally, because this dose and route of administration were best supported by the literature at the time of the development of our protocol.[3,10,26] Misoprostol can also be administered orally, rectally, buccally, or sublingually. Administration through the buccal route results in uterine tone and activity that are similar to those with the vaginal route,[27] and the sublingual route results in more rapid absorption and higher peak levels than the vaginal route.[28] When misoprostol is used to induce a first-trimester abortion, vaginal administration is more effective than oral administration and may have fewer side effects than the sublingual or buccal route.[29] Vaginal administration also permits efficacy at an interval of less than 24 hours after mifepristone administration among patients undergoing abortion.[25,30,31] Many of our participants chose not to wait the full 24 hours between mifepristone pretreatment and misoprostol use; future studies could test whether a shorter interval between the administration of these medications affects the efficacy of treatment for early pregnancy loss.

In 2000, the Food and Drug Administration first approved mifepristone for use with misoprostol to end an early pregnancy. This approval included Risk Evaluation and Mitigation Strategy requirements with the stated goal of mitigating the risk of serious complications associated with use of the drug. Although our study was not powered to show differences between groups in the proportions of serious adverse events, such events were rare — a finding that is consistent with the results of other published stud-

Table 3. Adverse Events among Women Who Received Medical Treatment for Early Pregnancy Loss.

Event	Mifepristone-Pretreatment Group (N=149)	Misoprostol-Alone Group (N=151)	Relative Risk or Incidence Rate Ratio (95% CI)*	P Value
Serious adverse events reported by participants				
Total number (rate per 100 women†)	5 (3.4)	3 (2.0)	1.68 (0.40–7.05)	0.47
Bleeding resulting in blood transfusion — no. of participants (%)	3 (2.0)	1 (0.7)	3.04 (0.32–28.6)	0.31
Pelvic infection — no. of participants (%)‡	2 (1.3)	2 (1.3)	1.01 (0.15–7.01)	0.99
Adverse events reported by participants				
Total no.	904	843		
Mean no. per participant	6.1	5.6	1.09 (0.99–1.19)	0.08
Type of event — no. of participants (%)				
Fatigue	118 (79.2)	115 (76.2)	1.04 (0.92–1.17)	0.53
Headache	88 (59.1)	72 (47.7)	1.24 (1.00–1.54)	0.05
Dizziness or lightheadedness	78 (52.3)	68 (45.0)	1.16 (0.92–1.47)	0.20
Chills	68 (45.6)	70 (46.4)	0.99 (0.77–1.26)	0.90
Nausea	56 (37.6)	56 (37.1)	1.01 (0.76–1.36)	0.93
Diarrhea	41 (27.5)	44 (29.1)	0.94 (0.66–1.35)	0.76
Vomiting	40 (26.8)	23 (15.2)	1.76 (1.11–2.79)	0.01
Severe cramping	20 (13.4)	21 (13.9)	0.97 (0.58–1.61)	0.90
Fever	10 (6.7)	9 (6.0)	1.12 (0.47–2.68)	0.79

* The rates for the total number of serious adverse events and mean number of adverse events were compared with the use of incidence rate ratios, with adjustment for trial site. The percentages of women who had each type of adverse event were compared with the use of relative risks that were adjusted for trial site with the Mantel–Haenszel method.
† The rate per 100 women is shown to account for the fact that a woman could have more than one event.
‡ Pelvic infection includes diagnoses of endometritis and septic abortion.

ies.[11,21,24,26,32] Studies of the use of mifepristone for induced abortion or for the treatment of early pregnancy loss have not shown a risk profile that supports such regulatory limitations on prescription.[33,34]

In conclusion, this randomized trial showed that pretreatment with mifepristone followed by treatment with misoprostol resulted in a higher likelihood of prompt and effective treatment of early pregnancy loss than misoprostol use alone.

Supported by the National Institute of Child Health and Human Development of the National Institutes of Health (Eunice Kennedy Shriver award number R01-HD0719-20 [to Dr. Schreiber] and Women's Reproductive Health Research award number K12-HD001265-18 [to Dr. Sonalkar]).

Dr. Creinin reports receiving consulting fees from Danco Laboratories. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the members of the PreFaiR trial team and the data and safety monitoring committee, the study participants for their dedication, and Dr. Alan D. Schreiber, without whom this research would not have been possible.

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Exhibit 4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Exhibit 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

DATE: March 28, 2016

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

THRU: (b) (6)

TO: (b) (6)

RE: NDA 020687, Supp 20

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

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

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

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/s/

(b) (6)

03/29/2016
adding to for the record

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

(b) (6)

(b) (6)

Date: March 29, 2016

(b) (6)

(b) (6) ((b) (6)

Subject: (b) (6) Assessment Review of the Year 4 risk evaluation and mitigation strategy (REMS) assessment report

Drug Name(s): Mifeprex® (mifepristone)

Therapeutic class: Progesterone-receptor modulator

Dosage forms: 200 mg tablets

(b) (6) Review Division: (b) (6)

Application Type/Number: NDA 020687, Supp 20

Applicant/sponsor: Danco Laboratories

This memo is to address specific statements made in the [redacted] ([redacted] Review of the Year 4 Risk Evaluation and Mitigation Strategy (REMS) assessment report that relate to an unapproved dosing regimen for Mifeprex.[1]

Mifeprex (NDA 20-687) is currently approved for the medical termination of intrauterine pregnancy through 49 days (7 weeks) gestation in a regimen with misoprostol. The currently approved dose of Mifeprex is 600 mg (three 200 mg) oral tablets which are to be taken under the supervision of a physician, followed two days later by two 200 mcg tablets (400 mcg) of misoprostol orally.

Danco Laboratories, LLC (Danco) submitted the 4 year REMS assessment report on June 2, 2015. The [redacted] REMS assessment reviewer had noted that there was use of the unapproved dosing regimen of Mifeprex 200 mg orally on day 1; followed by misoprostol 800 mcg, administered vaginally or buccally on day 3 or 4 for medical termination of intrauterine pregnancy up to 63 days gestation. The reviewer's comments included that it was unknown whether this unapproved regimen may have contributed to certain observed adverse events.

On May 29, 2015, Danco submitted a prior approval efficacy supplement-020 (PAS-020) seeking approval of certain changes to the approved indication, dosing regimen, and labeling for Mifeprex. Danco proposed to change the dosing regimen to: 200 mg orally x 1, instead of 600 mg orally x 1; followed 24-48 hours later by misoprostol 800 mcg, administered buccally; and an extension of gestational age from 49 to [redacted] 70 days). This supplement was under review at the time the October 2015 [redacted] REMS Assessment review was conducted.

The [redacted] ([redacted] is reviewing Danco's efficacy prior approval supplement-020 (PAS-020) to determine whether the supplement can be approved. Because [redacted] review encompasses all of the data and information submitted in the supplement, [redacted] defers to [redacted] with respect to the safety and efficacy of the dose and dosing regimen proposed by Danco.

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[1] [redacted] ([redacted] Review of Year 4 Risk Evaluation and Mitigation Strategy (REMS) Assessment Report, dated October 13, 2015

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(b) (6)

03/29/2016

memo to the assessment review

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
REMS Modification

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
(b) (6)
(b) (6)

NDA: 020687
PRODUCT: Mifeprex (mifepristone) oral tablets
APPLICANT: Danco Laboratories (Danco)
FROM: (b) (6)
DATE: March 29, 2016

This memorandum provides the (b) (6) ((b) (6) review of the proposed modifications to the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) addressed in the (b) (6) ((b) (6) REMS Modification Review and Addendum to REMS Modification Review. A REMS for Mifeprex was approved on June 8, 2011, to ensure the benefits of the drug outweighed the risks of serious complications. The Mifeprex REMS consists of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Mifeprex was approved for the medical termination of an intrauterine pregnancy through 49 days of gestation on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (Subpart H). It was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the 2007 Food and Drug Administration Amendments Act. A formal REMS proposal was submitted by Danco and approved on June 8, 2011. The goals and elements of the approved Mifeprex REMS are briefly summarized in Table 1 below.

Table 1. Summary of Mifeprex REMS[1]

REMS Goals	To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
	To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications.
REMS Elements	Medication Guide
	ETASU A – Special certification of healthcare providers (HCPs) who prescribe Mifeprex: Completion of Prescriber's Agreement form and enrollment in the REMS program.
	ETASU C – Mifeprex is dispensed only in certain healthcare settings: It is only available to be dispensed in clinics, medical offices or hospitals, under the supervision of a specially certified prescriber. Mifeprex will not be distributed to or dispensed through retail pharmacies.
	ETASU D – Safe-use conditions: Patients must complete and sign the Patient Agreement form that is to be placed in the patient's medical record. A copy of the Patient Agreement form and Medication Guide must be provided to the patient.
Implementation System	Distributors of Mifeprex must be certified and agree to ship Mifeprex only to locations identified by certified prescribers. Distributors must agree to maintain secure and confidential records, as well as, follow all distribution guidelines concerning storage, shipments and controlled returns.

[1] Source: The (b) (6) REMS Modification Review (NDA 20867/S-020, dated March 29, 2016), Table 1.

On May 29, 2015, Danco submitted an efficacy supplement (S-020) that proposed modifications to the Mifeprex Prescribing Information and REMS. In the S-020 submission, Danco seeks the following major changes (among others):

- [redacted] dosing regimen of Mifeprex and misoprostol
- Extension of maximum gestational age from 49 days to 70 days
- Replacement of the term "licensed physician" with "[redacted] in the REMS Prescriber's Agreement form
- Removal of the phrase "Under Federal Law" from the REMS Prescriber's Agreement form
- Revisions to the Patient Agreement form reflecting changes to the Prescribing Information

The proposed changes in the efficacy supplement prompted revisions to the Mifeprex REMS materials and also updating of the REMS materials to current format. During review of this efficacy supplement, we also evaluated the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure the drug benefits outweigh the risks. The Agency considered the recent [redacted] REMS Assessment review completed October 13, 2015, safety data gathered since drug approval in 2000, and experience from current clinical practice to support additional modifications to the Mifeprex REMS.

After consultations between the [redacted] and [redacted] and considering the [redacted] REMS Modification Review and Addendum to the REMS Modification Review, [redacted] has determined that the approved REMS for Mifeprex should be modified as follows:

1. Revisions to the Prescriber's Agreement form in addition to those proposed by the Applicant
2. Removal of the Medication Guide as a REMS element
3. Removal of the Patient Agreement form as a Documentation of Safe Use Condition (ETASU D)
4. Updating of REMS goals to reflect the above changes

We concur with [redacted] recommendation that the Prescriber's Agreement form should include other modifications to reflect current REMS standards and materials and also to reflect changes to align with approval of the efficacy supplement S-020, such as the dose and dose regimen and upper limit of gestational age.

In addition, we agree with Danco's proposed removal of the phrase "Under Federal Law," because of the lack of precedent for requiring such text and clinical rationale for its inclusion. As approvals and REMS are governed by Federal law, the phrase "Under Federal law" is unnecessary. Regarding Danco's proposal to replace "licensed physician," we have determined that the replacement term should be "licensed healthcare providers who prescribe," to include other practitioners who prescribe; in addition, this phrase is consistent with language in the statute.

We concur with [redacted] recommendation that the Medication Guide is no longer necessary as an element of the REMS to ensure the benefits of Mifeprex outweigh its risks. The Medication Guide will continue to be part of the approved labeling that must be provided to a patient in accordance with 21 CFR part 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

In addition, we concur with [redacted] recommendation that the signed Patient Agreement form is no longer necessary and should be removed as a condition of safe use (ETASU D). Recent professional guidelines for women seeking surgical and medical abortion services emphasize comprehensive counseling, education about the risks of different treatments, and obtaining and documenting informed consent.[2,3] The National Abortion

[2] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

Federation (NAF) clinical practice guidelines include a standard stating that documentation must show that the patient affirms that she understands the procedure and its alternatives, the potential risks and benefits, and that her decision is voluntary.[4] Approximately (b)(4)% of the use of Mifeprex in the U.S. is through Planned Parenthood Federation of America (PPFA)- and NAF-affiliated members, where patient counseling and informed consent is standard of care. The practice of treating women with Mifeprex is well-established by these organizations and their associated providers who choose to provide this care to women. In addition, the Medication Guide, which must be provided to the patient under 21 CFR part 208, contains the same risk information contained in the Patient Agreement form.

The safety profile of Mifeprex is well-characterized and its risks well-understood after more than 15 years of marketing. Serious adverse events are rare and the safety profile of Mifeprex has not substantially changed.[5] The removal of the Medication Guide as a REMS element and of the Patient Agreement form is not expected to adversely impact the ability of the REMS to ensure that the drug benefits outweigh its risks. The benefit-risk balance of Mifeprex remains favorable in the presence of the following:

- Retention of ETASUs A and C in the Mifeprex REMS: The Prescriber's Agreement form required for prescriber certification under ETASU A will continue to require that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This ensures that Mifeprex can only be dispensed by or under the direct supervision of a certified prescriber.

- Communication of risks through patient labeling: The Medication Guide, which will be retained as part of labeling, contains the same risk information covered under the Patient Agreement form. Under 21CFR 208.24, prescribers who dispense Mifeprex are required to provide the Medication Guide to patients. The Prescriber's Agreement form also reminds the prescriber to provide the Medication Guide to the patient.

- Information from published articles on established clinical practices: This information, including clinical guidelines and publications, indicates that comprehensive patient counseling and informed consent prior to medical or surgical abortion treatment is standard of care when using Mifeprex.

We have also determined that the information in the efficacy supplement supports changes to the goals of the Mifeprex REMS. We concur with (b)(6) recommendation that the REMS goals should be modified from:

A. To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
B. To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications.

to:

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

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

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[3] National Abortion Federation Membership information accessed on the internet at http://prochoice.org/health-care-professionals/naf-membership/ on March 11, 2016

[4] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf on March 11, 2016.

[5] (b)(6) Mifeprex Post-marketing Safety Review, dated August 20, 2015.

b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber.

The above REMS modifications and changes in goals were discussed with the [redacted] and concurrence with these changes was obtained.

The modified Mifeprex REMS should consist of ETASU A, in which healthcare providers who prescribe Mifeprex will be certified, and ETASU C, in which Mifeprex will be dispensed only in certain health care settings (specially clinics, medical offices, and hospitals) by or under the supervision of a certified prescriber. The Mifeprex REMS will also include an implementation system, and a timetable for continued submission of assessments of the REMS.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked [redacted] and [redacted] to continue to include a Patient Agreement form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through [redacted], the Director, OSE, and [redacted], to the Directors of [redacted] and [redacted]. Therefore, the Patient Agreement form will be retained and other changes will be made in the REMS to reflect that it is being retained, as described in the [redacted] Addendum to REMS Modification Review.

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/s/

(b) (6)

03/29/2016

Signing for (b) (6), (b) (6)

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

(b) (6)

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ADDENDUM TO REMS MODIFICATION REVIEW

Date:	March 29, 2016
Reviewer:	(b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
Subject:	Proposed REMS Modifications
Drug Name(s):	Mifeprex® (mifepristone)
Therapeutic class:	Progesterone-receptor modulator
Dosage forms:	200 mg tablets
(b) (6) Review Division:	(b) (6)
Application Type/Number:	NDA 020687, Supp 20
Applicant/sponsor:	Danco Laboratories
(b) (6) (b) (6) #:	2015-1719

1.

INTRODUCTION

This review is an addendum to the [redacted] March 29, 2016, REMS Modification Review regarding modifications to the risk evaluation and mitigation strategy (REMS) for Mifeprex, as proposed by Danco Laboratories in the amendment to the prior approval efficacy supplement 020 (PAS-20). See the March 29, 2016, REMS Modification Review for a description of the original submission and the existing REMS, and the materials informing our review.

In addition to those materials, we considered additional communications with the sponsor which included proposed changes to the REMS and REMS materials on March 21, 25, 27, 28 and 29th. We also considered a memorandum dated March 28, 2016 from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, requesting that [redacted] and [redacted] continue to include a Patient Agreement Form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through [redacted] This review addresses the sponsor's proposed changes as well as the changes that are needed in the REMS to reflect the fact that the Patient Agreement Form will be retained as part of the REMS.

This addendum will only describe changes that were recommended and that were not covered in the original REMS Modification Review. The changes we have agreed to were proposed to the sponsor and were accepted.

As with the original REMS modification review, all of the modifications discussed in this review were discussed with [redacted] and they are in agreement.

2. [redacted] AND SPONSOR PROPOSED MODIFICATIONS AND RATIONALE

2.1. REMS ELEMENTS

2.1.1. DOCUMENTATION OF SAFE USE CONDITIONS - ETASU D

2.1.1.1. PATIENT AGREEMENT FORM

As discussed above, it has been determined that the Mifeprex REMS should continue to include a Patient Agreement Form as ETASU D in the REMS. Therefore, the *Patient Agreement Form* is being revised as part of this modification.

The content has been modified to reflect the changes to the Prescribing Information that are being approved as part of the approval of PAS 020. These changes include changing the dosing regimen, updating the percentage of patients for which the treatment will not be effective, revising where Mifeprex or misoprostol should be taken and revising the patient follow-up recommendations after taking Mifeprex.

The requirement for a patient to read the MG has been removed since we are recommending that the MG be removed as an element of the REMS.[1] However, the MG will remain part of labeling

[1] [redacted] REMS Modification Review for Mifeprex, dated March 29, 2016.

and will still be required to be distributed to the patient as per 21 CFR part 208. In addition, certified HCPs will have agreed to provide a MG to the patient before providing Mifeprex.

Additionally, the reference to birth defects should be removed because the effects of Mifeprex on an ongoing pregnancy are unknown. Lastly, the attestation that the patient believes she is no more than a certain number of weeks pregnant should be removed. The Prescriber is responsible for accurately dating the pregnancy. Therefore, the patient should not be relied upon to date her own pregnancy.

2.2. REMS DOCUMENT

2.2.1. GOALS

As discussed in the REMS Modification Review dated March 29, 2016, the Mifeprex REMS goals should be modified. As discussed above, it has been determined that the Mifeprex REMS should continue to include the Patient Agreement Form, which is an ETASU D (documentation of safe use) requirement (see Section 4.1.1). Therefore, the goal of the REMS also should include objective c) below in underlined text.

> The goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by:
>
> a) Requiring healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program.
> b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber.
> c) Informing patients about the risk of serious complications associated with Mifeprex

(b) (4) The REMS goal should include the risks to be mitigated by the REMS. The phrase "risk of serious complications" was taken from the previously approved REMS document and continues to be applicable. (b) (6) recommends keeping the risks in the goal.

2.2.2. CERTIFICATION OF PRESCRIBERS - ETASU A

As discussed above, it has been determined that the Mifeprex REMS should continue to include the Patient Agreement Form. Therefore, ETASU A in the REMS document needs to be revised to reinsert information regarding this requirement. First, as was the case in the previously approved REMS document, certified prescribers must agree to review the Patient Agreement Form with the patient and answer any of her questions. Additionally, the prescriber must agree to sign the Patient Agreement Form and obtain the patient's signature on the form. Finally, the prescriber must agree to provide the patient with a copy of the Patient Agreement Form and insert a copy in the patient's chart. See redlined, attached REMS document.

In its March 21, 2016, submission, the Sponsor disagrees with changing the name of the *Prescriber's Agreement* to the *Prescriber Enrollment Form* because "enrollment" may be misconstrued by prescribers to mean they are being placed on a list or database. (b) (6) agrees

with the Sponsor's concern about using the term "Enrollment" in the title and proposes to change the name of the *Prescriber's Agreement* to the *Prescriber Agreement Form*. This has been reflected in the REMS document and the *Prescriber Agreement Form.*

The second proposed revision by the Sponsor applies to the qualifications of a certified prescriber. The REMS document currently states that prescribers must have the "ability to assess the duration of pregnancy accurately." Danco is proposing (b) (4) (b) (4) have concluded that not all practitioners are able to accurately assess gestational age. This ability is necessary for the safe use of Mifeprex.

In its March 21, 2016, submission, the Sponsor additionally proposed to insert "a non-identifiable reference" into the following statement in the REMS document and the *Prescriber Agreement Form* because it would increase the Sponsor's ability to track these adverse events. In addition, they stated that it is current practice for certified HCPs to provide this information. Danco also proposed removing "solely" from the statement, as shown below:

> Report any deaths to Danco Laboratories, identifying the patient ~~solely~~ by a non-identifiable reference and the serial number from each package of Mifeprex.

(b) (6) agreed with the above revisions. Lastly, the Sponsor proposed the following revised language in the REMS document and the Prescriber Agreement Form:

> …explain the risks (b) (4) of the ~~procedure, its effects, and the risks associated with~~ Mifeprex treatment regimen.

(b) (6) rejected the addition of (b) (4) to the REMS document and Prescriber Agreement Form. A REMS should only focus on the risks of a drug. Therefore, (b) (6) proposed that the final language be as follows:

> …explain the risks of the Mifeprex treatment regimen.

Additional minor edits and revisions were suggested for this section of the REMS document and corresponding language within the *Prescriber Agreement Form*. These changes were not intended to be substantive.

2.2.3. DOCUMENTATION OF SAFE USE CONDITIONS -ETASU D

As discussed above, it has been determined that the Mifeprex REMS should retain the Patient Agreement Form. Therefore, (b) (6) has proposed to insert the following text into the Mifeprex REMS document:

> 3. Mifeprex must be dispensed to patients with evidence or other documentation of safe use conditions.
>
> a. The patient must sign a *Patient Agreement Form* indicating that she has:
>
> i. Received, read and been provided a copy of the *Patient Agreement Form*.
>
> ii. Received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

2.2.4. IMPLEMENTATION SYSTEM

In its March 21, 2016, submission, the Sponsor proposed to [redacted] (b) (4)

a. Ship Mifeprex only to clinics, medical offices, and hospitals identified by certified prescribers in the signed *Prescriber Agreement Form*.

b. Complete the healthcare provider certification process upon receipt of the *Prescriber Enrollment Form.*

c. Notify healthcare providers when they have been certified by the Mifeprex REMS Program.

[redacted] (b) (6) [redacted] (b) (4). These are separate actions the distributor undertakes. Therefore, they should be described in the REMS document. Furthermore, it is not guaranteed that when a healthcare provider submits the *Prescriber Agreement Form*, they are ordering Mifeprex. In this situation, it is important that HCPs be notified when they are certified and, therefore, able to order Mifeprex in the future.

Lastly, [redacted] (b) (6) proposed to move the adverse event reporting requirements from the assessment to the implementation system of the REMS and to remove the requirement to report certain specifically enumerated adverse events such as all hospitalizations due to complications and women requiring transfusions, but retain the requirement to report all deaths. The following language was inserted:

"Danco Laboratories must report to FDA any death associated with Mifeprex 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 applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under the FDA regulations."

3. CONCLUSION

The review team and Sponsor have proposed additional modifications that continue to ensure that the benefit outweighs the risk for Mifeprex. This addendum addresses modifications to the REMS including those proposed by the sponsor in its March 21, 25, 27, 28 and 29, 2016, submissions, and additional changes recommended by [redacted] (b) (6) The additional changes include the following: reinsertion of the Prescriber Agreement Form (ETASU D) with certain changes to other documents to reflect this, and modification of the REMS goal, REMS document and appended materials provided to the Sponsor on March 17, 2016.

As discussed above, several changes to the language in the REMS document were proposed by Danco. The [redacted] (b) (4) were rejected by [redacted] (b) (6) The Sponsor additionally expressed their desire to not change the name of the *Prescriber's Agreement* to the *Prescriber Enrollment Form,* as suggested by the review team. In consideration of this, [redacted] (b) (6) proposes to change the title to the *Prescriber Agreement Form.*

The above changes to the REMS document and materials are appropriate modifications to the Mifeprex REMS. They are necessary to ensure that that the risks of serious complications will be mitigated and that the benefits of Mifeprex will continue to outweigh the risks.

4. RECOMMENDATIONS

The proposed amended modification submitted by Danco on March 29, 2016 is acceptable and (b) (6) recommends approval of the REMS.

Appendix

1. Prescriber Enrollment Form, clean
2. Patient Agreement Form, clean
3. REMS Document, clean

Initial REMS approval: 06/2011
Most recent modification: 03/2016

NDA 020687 MIFEPREX® (mifepristone) Tablets, 200 mg

Antiprogestational Synthetic Steroid

Danco Laboratories, LLC
PO Box 4816
New York, NY 10185

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

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

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

b) Ensuring that Mifeprex is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber.

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

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe Mifeprex must be specially certified.

   a. To become specially certified to prescribe Mifeprex, healthcare providers must:

      i. Review the Prescribing Information for Mifeprex.

      ii. Complete the *Prescriber Agreement Form*. By signing the *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 Mifeprex (see b.i-v below).

b. As a condition of certification, healthcare providers must follow the guidelines for use of Mifeprex described below:

i. Review the *Patient Agreement Form* with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
ii. Sign the *Patient Agreement Form* and obtain the Patient's signature on the *Form*
iii. Provide the patient with a copy of the *Patient Agreement Form* and Medication Guide.
iv. Place the signed *Patient Agreement Form* in the patient's medical record.
v. Record the serial number from each package of Mifeprex in each patient's record.
vi. Report any deaths to Danco Laboratories, identifying the patient by a non-identifiable reference and the serial number from each package of Mifeprex.

c. Danco Laboratories must:

i. Ensure that healthcare providers who prescribe Mifeprex are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements
ii. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

The following materials are part of the REMS and are appended:

- *Prescriber Agreement Form*
- *Patient Agreement Form*

2. Mifeprex must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

a. Danco Laboratories must:

i. Ensure that Mifeprex is available to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber.

ii. Ensure that Mifeprex is not distributed to or dispensed through retail pharmacies or other settings not described above.

3. Mifeprex must be dispensed to patients with evidence or other documentation of safe use conditions.
   a. The patient must sign a *Patient Agreement Form* indicating that she has:
      i. Received, read and been provided a copy of the *Patient Agreement Form*.
      ii. Received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

B. Implementation System

1. Danco Laboratories must ensure that Mifeprex is only distributed to clinics, medical offices and hospitals by or under the supervision of a certified prescriber by:

   a. Ensuring that distributors who distribute Mifeprex comply with the program requirements for distributors. The distributors must:

      i. Put processes and procedures in place to:

         a. Complete the healthcare provider certification process upon receipt of the *Prescriber Agreement Form.*

         b. Notify healthcare providers when they have been certified by the Mifeprex REMS Program.

         c. Ship Mifeprex only to clinics, medical offices, and hospitals identified by certified prescribers in the signed *Prescriber Agreement Form*.

         d. Not ship Mifeprex to prescribers who become de-certified from the Mifeprex Program.

         e. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who (1) attempt to order Mifeprex 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, proof of delivery and controlled returns of Mifeprex.

      iii. Train all relevant staff on the Mifeprex REMS Program requirements.

      iv. Comply with audits by Danco Laboratories, FDA or a third party acting on behalf of Danco Laboratories or FDA to ensure that all processes and procedures are in place and are being followed for the Mifeprex 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 Mifeprex.

2. Danco Laboratories must monitor distribution data to ensure compliance with the REMS Program.

3. Danco Laboratories must audit new distributors within 90 calendar days after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifeprex REMS Program. Danco Laboratories will take steps to address distributor compliance if noncompliance is identified.

4. Danco Laboratories must take reasonable steps to improve implementation of and compliance with the requirements of the Mifeprex REMS Program based on monitoring and assessment of the Mifeprex REMS Program.

5. Danco Laboratories must report to FDA any death associated with Mifeprex 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 applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

Danco Laboratories must submit REMS assessments to FDA one year from the date of the initial approval of the REMS (06/08/2011) and every three years 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 60 days before the submission date for that assessment. Danco Laboratories must submit each assessment so that it will be received by the FDA on or before the due date.

APPEARS THIS WAY ON ORIGINAL

PRESCRIBER AGREEMENT FORM

Mifeprex® (Mifepristone) Tablets, 200 mg

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 set up your account to receive Mifeprex, you must:
1. complete, 2. sign, and 3. fax page 2 of this form to the distributor.

If you will be ordering for more than one facility, you will need to list each facility on your order form before the first order will be shipped to the facility.

Prescriber Agreement: By signing page 2 of this form, you agree that you meet the qualifications below and will follow the guidelines for use. You also understand that if you do not follow the guidelines, the distributor may stop shipping Mifeprex to you.

Mifeprex must be provided by or under the supervision of a healthcare provider who prescribes and 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 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 Mifeprex. The Prescribing Information is available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Review the Patient Agreement Form with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
- 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 Mifeprex in each patient's record.
- Report deaths to Danco Laboratories, identifying the patient by a non-identifiable patient reference and the serial number from each package of Mifeprex.

ACCOUNT SETUP MIFEPREX® (Mifepristone) Tablets, 200 mg; NDC 64875-001-01

TO SET UP YOUR ACCOUNT:

1. Read the Prescriber Agreement on page 1 of this form.
2. Complete and sign this form.
3. Fax this page to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.
4. The distributor will call to finalize your account setup and take your initial order.
5. Subsequent orders may be phoned or faxed and are usually shipped within 24 hours.

Mifeprex® (Mifepristone) Tablets, 200 mg
THE ORIGINAL EARLY OPTION PILL

BILLING INFORMATION

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

SHIPPING INFORMATION ☐ *Check if same as above*

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

ADDITIONAL SITE LOCATIONS *I will also be prescribing Mifeprex* at these additional locations:*

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

REQUEST ADDITIONAL MATERIALS

☐ **Medication Guides** ☐ **State Abortion Guides** ☐ **Patient Brochures** ☐ **Patient Agreement Form**

ESTABLISHING YOUR ACCOUNT *(required only with first order)*

Each facility purchasing Mifeprex must be included on this form (*see additional site locations box above*) before the distributor can ship the product to the facility.

By signing below, you agree that you meet the qualifications and that you will follow the guidelines for use on page 1 of the Prescriber Agreement.

Print Name _____ Signature _____

Medical License # _____ Date _____

FAX THIS COMPLETED FORM TO THE AUTHORIZED DISTRIBUTOR. FAX: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

PATIENT AGREEMENT FORM

Mifeprex® (Mifepristone) Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of Mifeprex*. Both you and the patient must sign this form.*

Patient Agreement:

1. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take Mifeprex on Day 1.
   b. My provider will either give me or prescribe for me the misoprostol tablets which I will take 24 to 48 hours after I take Mifeprex.
3. My healthcare provider has talked with me about the risks including:
   - heavy bleeding
   - infection
   - ectopic pregnancy (a pregnancy outside the womb)
4. I will contact the clinic/office 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
   - severe stomach area (abdominal) pain
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - stomach pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
5. My healthcare provider has told me that these symptoms could require emergency care. If I cannot reach the clinic or office right away my healthcare provider has told me who to call and what to do.
6. I should follow up with my healthcare provider about 7 to 14 days after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
7. 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 Mifeprex and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
8. 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.
9. I have the MEDICATION GUIDE for Mifeprex. I will take it with me if I visit an emergency room or a healthcare provider who did not give me Mifeprex so that they will understand that I am having a medical abortion with Mifeprex.
10. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name (print):** _____ **Date:** _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for Mifeprex.

Provider's Signature: _____ **Name of Provider (print):** _____ **Date:** _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record.

03/2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

(b) (6)

03/29/2016

Concur

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

(b) (6)

(b) (6)

REMS MODIFICATION REVIEW

Date:	March 29, 2016
Reviewer:	(b) (4) (b) (6)
(b) (6)	(b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
Subject:	Proposed REMS Modifications
Drug Name(s):	Mifeprex® (mifepristone)
Therapeutic class:	Progesterone-receptor modulator
Dosage forms:	200 mg tablets
(b) (6) Review Division:	(b) (6)
Application Type/Number:	NDA 020687, Supp 20
Applicant/sponsor:	Danco Laboratories
(b) (6) (b) (6) #:	2015-1719

Table of Contents

1. INTRODUCTION 3
1.1 BACKGROUND 3
1.2 BRIEF SUMMARY OF KEY REGULATORY HISTORY 4
2. MATERIALS REVIEWED 4
3. OVERVIEW OF RATIONALE FOR proposed REMS MODIFICATIONS 5
4. Sponsor proposed modifications and Rationale 5
4.1. REMS ELEMENTS 5
4.1.1. Certification of Prescribers - ETASU A 5
4.1.1.1. Prescriber's Agreement 5
5. (b) (6) Proposed Modifications and Rationale 6
5.1. REMS ELEMENTS 6
5.1.1. Medication Guide 6
5.1.2. Certification of Prescribers - ETASU A 6
5.1.2.1. Prescriber's Agreement 6
5.1.3. Drug dispensed only in certain health care settings - ETASU C 7
5.1.4. Documentation of Safe Use Conditions - ETASU D 7
5.1.4.1. Patient Agreement 7
5.2. REMS DOCUMENT 8
5.2.1. GOALS 8
5.2.2. Medication Guide 9
5.2.3. Certification of Prescribers - ETASU A 9
5.2.4. Drug dispensed only in certain health care settings - ETASU C 9
5.2.5. Documentation of Safe Use Conditions -ETASU D 9
5.2.6. Implementation System 9
5.2.7. Timetable for Submission of Assessments 9
5.3. Assessment Plan 9
6. CONCLUSION 10
7. RECOMMENDATIONS 11
8. Appendix 11

1. INTRODUCTION

This review provides the [redacted] evaluation of the modifications to the risk evaluation and mitigation strategy (REMS) for Mifeprex proposed in the efficacy supplement submitted by Danco Laboratories (Danco) on May 29, 2015, and provides [redacted] recommendations to the [redacted] The approved REMS consists of a Medication Guide (MG), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The evaluation of modifications to the approved REMS utilized input received from the [redacted][1], REMS assessment data, and a postmarketing summary report by the [redacted]

1.1 BACKGROUND

Mifeprex is a synthetic steroid with antiprogestational effects. The currently approved dose is three 200 mg oral tablets which are to be taken under the supervision of a physician for the medical termination of intrauterine pregnancy through 49 days gestation. Mifeprex was approved September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (Subpart H).[2] 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. A formal REMS proposal was submitted by Danco and approved on June 8, 2011with a MG, ETASU, an implementation system and a timetable for submission of assessments. The goals and elements of the REMS are briefly summarized in Table 1 below.

Table 1. Summary of Currently Approved Mifeprex REMS

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

[1] [redacted]

[2] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

	To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications.
REMS Elements	Medication Guide
	ETASU A – Special certification of healthcare providers (HCPs) who prescribe Mifeprex: Completion of Prescriber's Agreement form and enrollment in the REMS program.
	ETASU C – Mifeprex dispensed only in certain healthcare settings: It is only available to be dispensed in clinics, medical offices or hospitals, by or under the supervision of a specially certified prescriber. Mifeprex will not be distributed to or dispensed through retail pharmacies.
	ETASU D – Safe-use conditions: Patients must complete and sign the Patient's Agreement form that is to be placed in the patient's medical record. A copy of the Patient's Agreement form and MG must be provided to the patient.
Implementation System	Distributors of Mifeprex must be certified and agree to ship Mifeprex only to locations identified by certified prescribers. Distributors must agree to maintain secure and confidential records, as well as, follow all distribution guidelines concerning storage, shipments and controlled returns.

1.2 BRIEF SUMMARY OF KEY REGULATORY HISTORY

A brief summary of the key regulatory history relevant to the Mifeprex REMS is listed below:

September 28, 2000: Mifeprex is approved with restricted distribution and postmarketing commitments under 21 CFR 314.520 (Subpart H).

September 27, 2007: FDAAA enacted and Mifeprex is deemed to have a REMS.

June 8, 2011: Mifeprex REMS is approved, NDA 020687/S-014

June 1, 2012: REMS Assessment Report, Year 1

June 2, 2015: REMS Assessment Report, Years 2-4

May 29, 2015: Danco submitted PAS- 020 efficacy supplement

January 15, 2016: A (b) (6) meeting was held to discuss proposed revisions to the REMS which included revising the REMS goal and removal of the MG and Patient Agreement form as elements of the REMS.

2. MATERIALS REVIEWED

2.1 SUBMISSIONS

- Danco Laboratories, Prior Approval Efficacy Supplement and REMS Modification, PAS-020, received May 29, 2015 (paper submission)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Mifeprex approval letter, dated September 28, 2000
- (b) (6) Mifeprex PAS-014 approval letter, dated June 8, 2011
- (b) (6) Final deemed REMS Review for Mifeprex:, dated June 3, 2011
- (b) (6) Review of Year 1 REMS Assessment Report: dated August 1, 2012
- (b) (6) Review of Year 4 REMS Assessment Report: dated October 13, 2015

- (b) (6) Mifeprex Post-marketing Safety Review: dated August 20, 2015
- Addendum to (b) (6) Review of Year 4 REMS Assessment Report: dated March 29, 2016
- (b) (6) draft Clinical Review for Mifeprex, NDA 020687, PAS 20: dated March 29, 2016.

3. OVERVIEW OF RATIONALE FOR PROPOSED REMS MODIFICATIONS

On May 29, 2015, Danco submitted an efficacy prior approval supplement-020 (PAS-020) and REMS modification. In PAS-020, Danco is seeking approval of certain changes, including:

- Dosing of 200 mg orally x 1, instead of 600 mg orally x 1
- Extension of maximum gestational age
- Inclusion of misoprostol in the indication statement
- Inclusion of information regarding Pediatric Research Equity Act (PREA) data
- Replacement of the term "physician" with " (b) (4) in the PI and the REMS Prescriber's Agreement
- Removal of the phrase "Under Federal Law" from the REMS Prescriber's Agreement
- Revisions to the Patient Agreement Form to reflect proposed changes in the PI

The Sponsor's proposed changes in the efficacy supplement prompted revisions to the Mifeprex REMS materials. During review of the efficacy supplement and proposed REMS Modifications, (b) (6) evaluated the current REMS program to determine whether other changes were appropriate. As part of this evaluation, the review team took into consideration the recent (b) (6) review of the Mifeprex REMS Assessment completed on October 13, 2015, the addendum to the October 13, 2015 review completed on March 29, 2016, safety data gathered over the past 16 years since approval, and information regarding current clinical practice.[5,6,8,9]

Based on the available data and information, (b) (6) continues to believe that a REMS is necessary to ensure the benefits outweigh the risks; however, we recommend that some elements be modified or removed. All of the modifications in this review were discussed with (b) (6) The recommended modifications and supporting rationale for each are further described in Sections 4 and 5 below.

4. SPONSOR PROPOSED MODIFICATIONS AND RATIONALE

4.1. REMS ELEMENTS

4.1.1. CERTIFICATION OF PRESCRIBERS - ETASU A

4.1.1.1. PRESCRIBER'S AGREEMENT

Danco is proposing two modifications to the Prescriber's Agreement form. The first proposal is to remove the phrase "Under Federal law" from the document. This phrase appears twice in the Prescriber's Agreement:

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

The Sponsor is proposing that the phrase be deleted from the beginning of the above sentences to be consistent with current REMS language.

Reviewer Comment: The review team agrees with this revision. The review team has determined that there is no precedent in other REMS for using the phrase, nor is there any clinical rationale for including it. As approvals are governed by Federal law, the review team concludes that the phrase "Under Federal law" is unnecessary in the Prescriber's Agreement.

The second proposed modification from Danco is to replace the word "physician" with "(b) (4) The Prescriber's Agreement currently reads: "Under Federal law, Mifeprex must be provided by or under the supervision of a *physician* who meets the following qualifications…" The Sponsor is proposing that the agreement read: "Mifeprex must be provided by or under the supervision of a (b) (4) who meets the following qualifications…"

Reviewer Comment: The review team agrees that the term "physician" should be replaced, but with the phrase "healthcare provider who prescribes." '(b) (4) . Mifeprex is a prescription medication and "healthcare providers who prescribe" accurately describes not only physicians but other healthcare providers, for example, nurse practitioners, certified nurse midwives and physician assistants, who may prescribe medications. Additionally, the phrase "healthcare provider who prescribes" is consistent with the language that is included in the statute.[3]

5. (b) (6) PROPOSED MODIFICATIONS AND RATIONALE

5.1. REMS ELEMENTS

5.1.1. MEDICATION GUIDE

FDA has generally been maintaining MGs as FDA-approved labeling but removing them from REMS when inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks. The Mifeprex MG, though an important tool for patient education that will continue to be distributed to patients, does not need to be an element of the REMS to ensure the benefits outweigh the risks for Mifeprex. The MG will remain part of labeling and will still be required to be distributed to the patient as per 21 CFR part 208. This approach is consistent with ongoing efforts to streamline REMS by allowing for changes to a MG without the need for a REMS modification.

5.1.2. CERTIFICATION OF PRESCRIBERS - ETASU A

5.1.2.1. PRESCRIBER'S AGREEMENT

Per the current Mifeprex REMS, a Prescriber's Agreement is required to be completed, signed and faxed to the distributor to complete enrollment. The review team is recommending

[3] FDCA 505-1(f)(3)(A).

changing the name of the form from "Prescriber's Agreement" to "Prescriber Agreement Form" to be consistent with the terminology used in other similar REMS Programs. The term *"physician"* should be replaced, as proposed by the Sponsor. However the review team recommends the phrase "*healthcare provider who prescribes*" in lieu of the Sponsor proposed "(b) (4) to more closely reflect the statutory provision, and to align with this revision in the Mifeprex Prescribing Information (PI), which was based on information in the supplement.[4] Additional changes are intended to improve the flow of the document. See the appended, redlined document for further details.

Consistent with the labeling revisions in the efficacy supplement, the language in the Prescriber Enrollment Form about the gestational age should be changed to match the labeling being approved.

5.1.3. DRUG DISPENSED ONLY IN CERTAIN HEALTH CARE SETTINGS - ETASU C

No changes to ETASU C are proposed.

5.1.4. DOCUMENTATION OF SAFE USE CONDITIONS - ETASU D

5.1.4.1. PATIENT AGREEMENT

Per the Mifeprex REMS, a Patient Agreement form is required to be signed and placed in the patient's medical record as documentation of safe use conditions for Mifeprex. The review team recommends removal of the Patient Agreement form from the Mifeprex REMS. This recommendation is based in part on the fact that the current Patient Agreement is duplicative of the informed consent and counseling processes that take place in the US, consistent with medical standard of care and current clinical practice guidelines for abortion providers.[5,6,7] For example, the National Abortion Federation (NAF) clinical practice guidelines state that "obtaining informed consent and assessing that the decision to have an abortion is made freely by the patient are essential parts of the abortion process." The NAF guidelines also include a standard stating that documentation must show that the patient affirms that she understands the procedure and its alternatives, the potential risks and benefits, and that her decision is voluntary.[6] The NAF is a professional association; a condition of membership requires periodic quality assurance site visits, and members must agree to adhere to the Clinical Policy Guidelines published by the NAF.[7] When healthcare providers at NAF affiliated facilities were surveyed, between 96 and 99% of healthcare providers indicated they provided patient counseling and obtained and documented informed consent.[8,9] The review team is aware that

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[4] (b) (6) draft Clinical Review for Mifeprex (NDA 020687) PAS 20. Dated: March 29, 2016

[5] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

[6] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf on March 9, 2016.

[7] National Abortion Federation Membership information accessed on the internet at http://prochoice.org/health-care-professionals/naf-membership/ on March 9, 2016

[8] Gould H, Perrucci A, Barar R, Sinkford D, Foster D. Patient Education and Emotional Support Practices in Abortion Care Facilities in the United States. Women's Health Issues 2012; 22-4; 359-364

Planned Parenthood of America has informed consent forms describing the risks associated with medical abortions. The NAF affiliated members and Planned Parenthood of America facilities account for (b) (4)% of Mifeprex use.

The information in the Mifeprex REMS Patient Agreement form is duplicative of the informed consent process that is followed and documented by these providers, who also provide abortion counseling and education about adverse events. Additionally, the MG, which is required to be provided under 21 CFR 208, contains the same risk information addressed in the Patient Agreement form and will be provided at the time the medication is dispensed to the patient. Based on this information, the Patient Agreement form is not necessary to ensure the benefits outweigh the risks of Mifeprex.

Finally, the U.S. marketing history of Mifeprex spans over fifteen years. During this period of surveillance, the safety profile of Mifeprex has been well-characterized, and serious adverse events have rarely occurred. [10,11,12]

5.2. REMS DOCUMENT

The REMS document is being revised to reflect the changes described above as well as to reflect the Agency's current thinking on the language and flow in REMS documents. The changes to the different sections of the REMS document are described further below. For additional details, see the redlined and clean REMS document appended to this review.

5.2.1. GOALS

The review team is recommending modification of the Mifeprex REMS goals. Currently the goals are (A) to provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and (B) to minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications. Since (b) (6) is recommending removal of the Patient Agreement from the REMS, (b) (6) recommends revising the REMS goals to reflect this change. The revised goal is to ensure that prescribers are aware of the risks of serious complications associated with the use of Mifeprex and that it can only be dispensed in certain health care settings. The goal would be modified to read:

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[9] O'Connell K, Jones HE, Simon M, Saporta V, Paul M, Lichtenberg ES. First trimester surgical abortion practices: a survey of National Abortion Federation members. Contraception 2009; 79:385-392

[10] (b) (6) ((b) (6) Mifeprex Post-marketing Safety Review: (b) (6), dated August 20, 2015

[11] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

[12] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf

"The goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by:

a) Requiring healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program.
b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber."

5.2.2. MEDICATION GUIDE

(b) (6) recommends this element be removed from the REMS document. See Section 5.1.1 for rationale.

5.2.3. CERTIFICATION OF PRESCRIBERS - ETASU A

The language in the REMS document stating that certified prescribers must obtain a completed Patient Agreement form from the patient is recommended to be removed (see Section 5.1.2.1 for rationale). In addition, edits to align the REMS document with language in the revised PI are being made. Finally, we recommend that this section of the REMS document be revised and edited to reflect the Agency's current thinking on the most appropriate language and flow of REMS documents. However, the requirement for Prescriber Certification remains and the qualifications of a healthcare provider who prescribes Mifeprex have not changed and continue to be necessary to ensure the benefits outweigh the risks.

5.2.4. DRUG DISPENSED ONLY IN CERTAIN HEALTH CARE SETTINGS - ETASU C

This section of the REMS was edited to provide clarification on where Mifeprex will not be dispensed.

In addition, the REMS document was revised and edited to reflect (b) (6) current thinking on the language and flow of REMS documents. These changes are not intended to be substantive.

5.2.5. DOCUMENTATION OF SAFE USE CONDITIONS -ETASU D

This element is being recommended for removal from the REMS document. See section 5.1.4.1 for rationale.

5.2.6. IMPLEMENTATION SYSTEM

This section of the REMS document is proposed to be revised and edited to reflect the Agency's current thinking on the language and flow of REMS documents.

5.2.7. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

This section of the REMS document is proposed to be revised and edited to reflect the Agency's current thinking on the language and flow of REMS documents.

5.3. ASSESSMENT PLAN

Currently, the REMS Assessment Plan requires Danco to submit the following adverse event information as part of the periodic REMS Assessment Report:

> 6. Copies of MedWatch forms for each of the following adverse events during the assessment period; and for each of the following adverse events, the cumulative number from the date of approval of Mifeprex up to the approval date of the REMS, the number for each reporting period, and the cumulative number since the approval date of Mifeprex:
>
> a. On-going pregnancies not terminated subsequent to the conclusion of the treatment procedure
> b. Women hospitalized due to complications
> c. Women requiring transfusion(s) of two or more units of packed cells or whole blood, or having a hemoglobin of 6 gm/dL or less or a hematocrit of 18% or less
> d. Serious infection, sepsis
> e. Death
> f. Other serious and unexpected adverse events
>
> 7. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue.

This information is being submitted to the Agency through other pathways including spontaneous adverse event reporting and the annual report. Therefore, (b) (6) is recommending it be removed from the Assessment Plan.

The revised Assessment Plan is as follows:

REMS Assessment Plan

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative)
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

6. CONCLUSION

A REMS for Mifeprex is necessary to ensure that the benefits outweigh the risks. The review team and Sponsor have proposed modifications that continue to ensure that the benefit outweighs the risk, while updating the REMS in light of current medical practice and to provide clarifying language in the REMS documents.

The modifications to the Mifeprex REMS include the sponsor's proposed modifications and additional changes recommended by the review team and include the following: revision of the REMS goals, removal of the MG (it will remain as part of labeling) and the Patient Agreement; and changes to the Prescriber Enrollment Form.

7. RECOMMENDATIONS

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

8. APPENDIX

1. Prescriber Enrollment Form, redlined
2. Prescriber Enrollment Form, clean
3. REMS Document, redlined
4. REMS Document, clean

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Exhibit 5

Contraception 104 (2021) 24–28

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Mifepristone restrictions and primary care: Breaking the cycle of stigma through a learning collaborative model in the United States

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ABSTRACT

Despite its safety record, mifepristone is subject to a highly restrictive set of regulatory measures through the Risk Evaluation and Mitigation Strategy (REMS) by the US Food and Drug Administration. We argue that these restrictions both reflect and perpetuate a cycle of abortion stigma, creating particular barriers to mifepristone use in primary care settings where communities that historically experience barriers to care can most easily access reproductive health services. Through qualitative interviews with Illinois primary care clinicians, we discovered how the REMS heightens institutional anxiety over implementation of mifepristone use. To address this, we created *ExPAND Mifepristone*, a learning collaborative targeting institutional anxiety and logistical barriers to mifepristone use. The learning collaborative model holds high potential to mitigate institutional barriers to mifepristone use by increasing providers' self-efficacy to identify, address, and overcome institutional fears. Until the REMS is fully repealed, learning collaboratives constitute a promising tool to combat the practical and psychological barriers to mifepristone use that these restrictions currently pose.

Introduction

Abortion with mifepristone is safe and effective [1–4]. This treatment falls well within the scope of primary care in the United States, as it involves patient assessment and health education for which primary care providers are extensively trained [5–8]. Nonetheless, many clinicians trained to provide medication abortion do not currently do so, and only an estimated 1% of medication abortions occur in primary care offices [9,10]. The potential for primary care providers to help improve abortion access is particularly high in the Midwest, which experienced the largest regional decline in abortion clinics over the past decade [11]. Given this context, our team set out to develop an evidence-based intervention to support mifepristone use in primary care in Illinois, resulting in the learning collaborative *Excellence in Providing Access to New Directions in Mifepristone Use* (*ExPAND Mifepristone*). This commentary describes how *ExPAND Mifepristone* seeks to disrupt a cycle of abortion stigmatization in primary care that is anchored by the US Food and Drug Administration's inclusion of mifepristone in the Risk Evaluation and Mitigation Strategy (REMS) program. We argue that the REMS serves as the linchpin of a cycle of medication abortion stigmatization in primary care, encouraging institutional anxiety over abortion provision which leads to logistical barriers to mifepristone use. This cycle successfully excludes mifepristone from many primary care settings, reinforcing the perception that abortion is a tainted and undesirable service that should remain marginalized in specialty settings. The learning collaborative model serves as a potentially valuable framework for primary care physicians to address, understand, and overcome the institutional fears that the REMS program encourages.

1. The mifepristone REMS and the ripple effect of logistical barriers

*The fascinating thing is, there are a lot of other things I've managed to implement [*since joining this primary care practice*], and when the perception is that your organization does not care, or prioritize providing abortion care, the barriers can be great, and other [*services*] the organization does prioritize, the resources, the people, the organization gets behind them. So it's very frustrating to me that abortion care again occupies this separate space.* – Illinois primary care provider

The REMS for mifepristone requires that (1) the drug be dispensed in healthcare settings by or under the supervision of a cer-

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0010-7824/

Exhibit 5

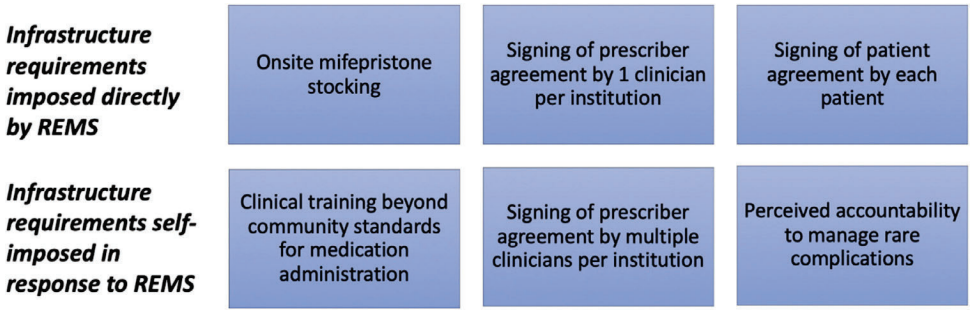

Fig. 1. Taxonomy of barriers to medication abortion care in primary care settings.

tified prescriber; (2) dispensing clinicians register with the drug manufacturer; and (3) patients sign a specific form stating the drug will be used for a medication abortion, despite the evidence base that it is also effective for both early pregnancy loss treatment and cervical ripening for dilation and evacuation procedures [12–14]. While the REMS program aims to reduce risks from drugs with high potential of serious adverse health effects [15], mifepristone has been shown to have an excellent safety profile [16]. As a result, mifepristone access has expanded globally through evidence-based deregulation. Mifepristone is fully incorporated in abortion services in Canada, as the federal regulatory system permits dispensing through a pharmacy with a prescription from a clinician and no longer requires an ultrasound prior to prescribing [17,18]. Mifepristone distribution via postal mail following a telemedicine appointment is also approved in the United Kingdom [19]. In light of these regulatory frameworks, the REMS stands out as exceptionally restrictive.

To gain a more comprehensive understanding of the institutional barriers primary care providers face to evidence-based mifepristone use, we conducted a qualitative study of providers in Illinois and assessed their opinions of the REMS restrictions and other barriers to medication abortion provision. As part of this larger study on barriers to abortion provision in primary care, 19 primary care providers and clinical administrators participated in semi-structured interviews exploring barriers to and facilitators of mifepristone use at the individual, institutional, and policy levels. We sampled clinicians based on their current abortion provision status (providing in primary care or not), type of health care facility (community health center, hospital, group or private practice), and geographic location (within vs. outside of Chicago). For full study methodology, see Rasmussen and colleagues, this issue.

Overall, interviewees expressed widespread support of removal of the mifepristone REMS and reported that removing the REMS would help them or their colleagues integrate medication abortion into primary care. We noted that providers named two types of barriers posed by the REMS: direct infrastructure requirements for dispensing mifepristone; and requirements self-imposed in response to the REMS (Fig. 1). On a practical level, some clinicians expressed that if the REMS was eliminated and they could prescribe mifepristone through a pharmacy, that would remove logistical barriers around medication stocking [20]. Participants also expressed that the REMS impedes mifepristone use in primary care by perpetuating fear and mystery around the drug that is not supported by clinical evidence of its risks, resulting in the desire for excessive clinical training, unnecessary bureaucratic infrastructure-building, and fear of extremely rare complications with mifepristone use. The resulting institutional anxiety around abortion provision drives a process of stigmatization of which the REMS forms an integral part.

2. Logistical barriers within a cycle of stigmatization

Interviewer: Your practice has implemented quite a few new services. How do you feel implementing these services is analogous or different to implementing abortion?

Clinician: I want to say it's just the stigma that surrounds it is the only real difference. When there's money…and operations stand behind it, it's much easier, but then we are also now faced with the…stigma of it. – Illinois primary care provider

The REMS program imposes medically unnecessary restrictions on mifepristone access, and these restrictions create specific logistical hurdles, as well as generating an impression that provision of mifepristone is difficult and requires extensive training, ultimately creating a hesitancy among primary care clinicians to administer it. As illustrated in Figure 2, the REMS are the linchpin of a cycle of stigmatization that continues to keep mifepristone out of primary care practice and other non-specialty settings over time. Similarly to stigma among abortion patients and providers, institutional stigma around abortion care functions as a cycle [21,22]. Because regulations such as the REMS are imposed, institutions perceive abortion care to be excessively complex, and fear abortion provision. Out of fear, leadership blocks qualified clinicians from integrating abortion into their primary care practice. Thus, abortion remains siloed from mainstream medicine, reinforcing the perception that it is a tainted medical practice [23].

We heard this hesitancy in our interviews, as clinicians expressed concern over their own competency to administer mifepristone to their patients. When asked about their personal barriers to administering medication abortion, one clinician responded: "I totally believe that it can be done, but I also feel like I didn't have that preparation… But I've heard that some people do it in primary care settings…I'm like, 'How do I do this? Can I do it?'" Other clinicians expressed feeling a sense of hypervigilance when it came to providing medication abortion services because of the seemingly specialized nature of mifepristone protocols. One clinician noted their heightened sense of alertness stems from their desire to distribute mifepristone perfectly. They commented: "I think there's a piece of perfectionism…it may lead us to stumble across smaller roadblocks, because we're looking for a perfect outcome, rather than a safe and acceptable outcome." As a result of the perceived need for extensive training in medication abortion provision, primary care institutions lean towards not administering mifepristone in fear of incorrectly distributing the medication or not knowing how to proceed with potential adverse side effects. While primary care institutions see training as necessary to overcome institutional anxiety about abortion provision, this anxiety can also prevent individuals from accessing additional training: "Even just talking about wanting abortion training or having that be a conversation that felt normal was a barrier because of the stigma around abortions."

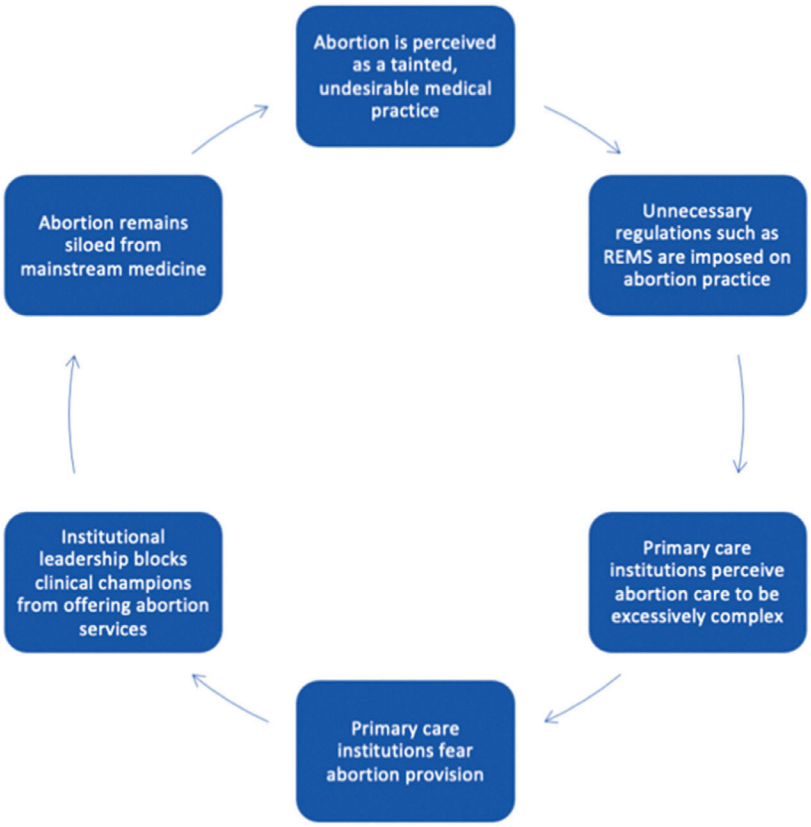

Fig. 2. Cycle of abortion stigmatization in primary care.

This institutional anxiety directly feeds into implementation challenges, as some interview participants expressed a desire to implement medication abortion in their clinics but an unwillingness among institutional leadership to allow this service. One respondent commented, "We've been unable to get... even though there are pathways for doing medication abortion…sadly, our board…doesn't feel comfortable. They're afraid." Many interviewees named budget constraints as a main reason for not providing medication abortion services, as clinicians working in federally qualified health centers (FQHCs) have very limited funding that they cannot afford to waste. Because the REMS requires onsite drug stocking rather than pharmacy prescription, providers expressed that clinical leadership hesitated to invest funds in the medication given their very limited resources. One clinician commented: "So it's kind of, yeah, we want to, but is that a necessary thing to do to take time and money and resources away from the rest of…what the FQHC is doing." These implementation barriers, combined with institutional anxiety, create a cycle of abortion stigmatization that isolates medication abortion from mainstream medicine. Removal of the REMS would disrupt this cycle significantly by alleviating the need for infrastructure-building within clinics and signaling leadership that the drug is safe enough to be prescribed without excessive training. However, in the current context of having the REMS in place, we identified a structured, multi-institutional learning collaborative as a promising strategy to disrupt the stigma cycle and help clinics overcome both the logistical and the psychological barriers at play.

3. Opportunity for action within the learning collaborative model

*I wish that [*abortion implementation*] would have been the same way that I participated in other quality collaboratives, whether it's to improve depression care, hypertension care, implement new screening, protocols…A big part of my career now has become working in quality improvement. There are best practices out there for how to do this, for how to help organizations across the country, who are trying to do the same thing.* -Illinois primary care clinician

In our formative research, clinicians described how mifepristone distribution is seen as a complex process that requires extensive training and experience to dispense. These findings highlight the need for evidence-based interventions in primary care, leading us to create *ExPAND Mifepristone*, a learning collaborative geared towards disrupting the stigma around mifepristone use for both abortion and miscarriage management in primary care settings. *ExPAND Mifepristone* launched in spring 2020 and aims to demystify mifepristone use in clinical care by building self-efficacy and knowledge not only around clinical applications of the drug, but also regarding billing, stocking, scheduling, and other logistical barriers. This program is largely based on the learning collaborative model developed by the Institute for Healthcare Improvement's Breakthrough Series. The learning collaborative model is defined as a 6-to-15-month intervention that provides a structure for organizations to learn from each other in multidisciplinary teams on a certain issue [24]. In addition to creating collaborative teams within organizations, learning collaboratives generally include highly skilled experts to educate and train the teams to incorporate changes within their settings. This training is then followed by an action period where the teams implement the changes and report back to the learning collaborative, allowing experts to weigh in on their progress and for other teams to learn from each other. The learning collaborative approach is proven to be successful in fostering implementation of evidence-based practices across a wide range of clinical settings serving both children and adults [25,26]. In the field of reproductive health care in particular, the learning collaborative model has improved care and ed-

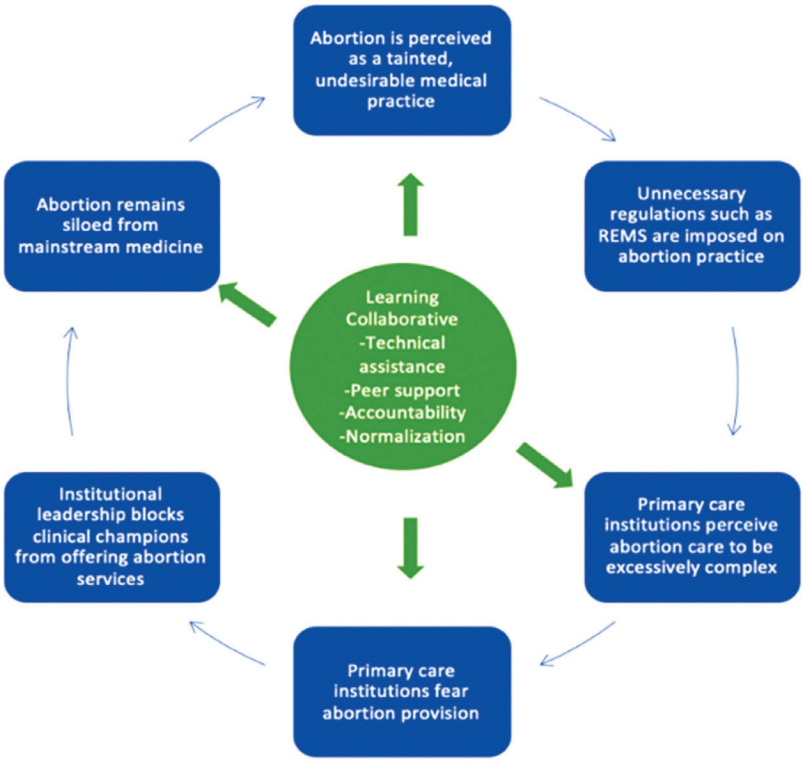

Fig. 3. Cycle of stigmatization of abortion in primary care—Hypothesized impact of a learning collaborative intervention.

ucation for individuals with preeclampsia and for individuals with postpartum gestational diabetes [27,28].

Drawing on the literature of best practices for learning collaboratives more broadly, we designed the *ExPAND Mifepristone* collaborative specifically to target the cycle of stigma while helping clinics build infrastructure for full-spectrum evidence-based mifepristone use (Fig. 3). The program is designed to provide clinicians with concrete tools to incorporate mifepristone in primary care settings in Illinois through monthly group meetings, on-site and distance consultation, self-assessment, and tailored evaluation. The *Expand Mifepristone* learning collaborative includes expert coaches who advise physicians and administrators on how to combat institutional hurdles and competing priorities to incorporate mifepristone in their clinics. Trainings in our pilot year shared new evidence-based guidelines for early pregnancy loss and no-test medication abortion [29,30] and provided guidance on how primary care clinicians can bill for mifepristone. Illinois law provides for public and private insurance coverage of abortion [31,32], and the collaborative clarified the funding component of abortion provision through trainings on Medicaid reimbursement policies and procedures. The collaborative also provided expert, step-by-step support in understanding and navigating the process of registering with the manufacturer(s) to dispense mifepristone, as well as understanding how to use required patient consent forms and how to enable in-office dispensing of mifepristone. This implementation-based training was designed to debunk the misconceptions associated with mifepristone.

Based on our conceptual model of how abortion stigma inhibits abortion provision in primary care (Fig. 2), we hypothesize that by the end of the program, clinicians should be equipped with enhanced self-efficacy around mifepristone use, as well as the concrete logistical tools needed to provide mifepristone for abortion and miscarriage management in primary care. We are testing these hypotheses through a mixed-methods evaluation with qualitative interviews and review of electronic medical record data from *ExPAND Mifepristone*'s pilot clinics. We will apply an implementation science framework to our analyses, to refine the program's design for future cohorts.

4. Moving forward: Deregulate, educate, and empower primary care clinicians

The *ExPAND Mifepristone* learning collaborative constitutes a potential model for mitigating medication abortion stigma specifically and mifepristone stigma more broadly in primary care settings by addressing both logistical and psychological barriers. The existence of the REMS diffuses stigma within primary care settings and encourages hesitation and fear amongst clinicians and administrators to provide abortion. While the learning collaborative model addresses the stigmatization that is driven by the REMS, removal of mifepristone from the REMS program would likely have a far greater impact on abortion stigma. Nonetheless, as stigma operates at multiple levels across medical training, institutions, and the broader social context, even in the absence of the REMS, additional work will be needed to normalize abortion in primary care [21–23,32–35].

ExPAND Mifepristone represents just one potential approach to supporting clinical champions of mifepristone use in primary care in taking on institutional barriers to evidence-based use. To complement the existing robust infrastructure to train primary care providers in pregnancy diagnosis and management, including abortion care [8,36–37], additional programs to support implementation of medication abortion in primary care should be created and evaluated over time. As the largest and most geographically well distributed provider group in the United States, primary care providers hold immense untapped potential to expand abortion access. Unless and until the US health care system joins the global trend of mifepristone deregulation, learning collaboratives and other systems of practical support can empower clinicians

to overcome logistical barriers to providing the holistic, patient-centered pregnancy care their patients deserve.

Declaration of competing interest

None.

Funding

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Acknowledgments

The authors thank Noel Leon for introducing us to the phrase "institutional anxiety." We also thank Alischer Cottrill, Ashley McHugh, and Ellen McCammon for their roles in the formative research that inspired *ExPAND Mifepristone.* We are grateful to our *ExPAND* expert consultants Kristie Monast, Susan Rubin, and Julie Gonen, and to the clinics participating in the program's pilot year.

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Exhibit 6

Disparities and change over time in distance women would need to travel to have an abortion in the USA: a spatial analysis

Jonathan M Bearak, Kristen Lagasse Burke, Rachel K Jones

Summary

Background Abortion can help women to control their fertility and is an important component of health care for women. Although women in the USA who live further from an abortion clinic are less likely to obtain an abortion than women who live closer to an abortion clinic, no national study has examined inequality in access to abortion and whether inequality has increased as the number of abortion clinics has declined.

Methods For this analysis, we obtained data on abortion clinics for 2000, 2011, and 2014 from the Guttmacher Institute's Abortion Provider Census. Block groups and the percentage of women aged 15–44 years by census tract were obtained from the US Census Bureau. Distance to the nearest clinic was calculated for the population-weighted centroid of every block group. We calculated the median distance to an abortion clinic for women in each county and the median and 80th percentile distances for each state by weighting block groups by the number of women of reproductive age (15–44 years).

Findings In 2014, women in the USA would have had to travel a median distance of 10·79 miles (17·36 km) to reach the nearest abortion clinic, although 20% of women would have had to travel 42·54 miles (68·46 km) or more. We found substantially greater variation within than between states because, even in mostly rural states, women and clinics were concentrated in urban areas. We identified spatial disparities in abortion access, which were broadly unchanged, at least as far back as 2000.

Interpretation We showed substantial and persistent spatial disparities in access to abortion in the USA. These results contribute to an emerging literature documenting similar disparities in other high-income countries.

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See Comment page e484

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Introduction

Induced abortion allows women to control their fertility, and ensuring that all women in the USA have access to abortion is a public health goal.[1,2] In 2011, 2·8 million (45%) of the 6·1 million pregnancies in the USA were unintended, and 42% of unintended pregnancies ended in abortion.[3] However, abortion is not always easy to access in the USA, and issues such as stigma, restrictive laws, and financial constraints can pose barriers to access. One key measure of access is how far women have to travel to reach an abortion clinic. Previous research[4–7] found that the further a woman lives from a provider, the less likely she is to obtain an abortion. Most patients seeking an abortion have limited financial resources, so having to cover the cost of travel (which can include overnight stays and time off work) might prevent them from having an abortion.[8]

Spatial inequality—unequal access to resources and services based on location—affects access to abortion in many countries where it is legal.[9] Studies[10–13] in Australia, New Zealand, Canada, and the USA have found that, among women who have abortions, those who live in rural areas typically travel greater distances than those who live in urban areas, at least in part because of subnational variation in restrictive laws.[13]

At least 20 US states have adopted one or more abortion restrictions since 2011 (appendix), making analysis of spatial inequality in that country particularly timely and relevant.[14] In 2008, patients in the USA travelled a median distance of 15 miles (24 km) to have an abortion.[15] Although the median distance travelled was reasonably low, a substantial minority of women (17%) travelled 50 miles (80 km) or more, and 31% of women living in rural areas travelled 100 miles (161 km) or more to have an abortion. A 2016 study[16] examined the change in how far women travelled for an abortion in the state of Texas after implementation of a restrictive law, which resulted in the closure of 22 (54%) of 41 abortion providers in the state. Similar to women nationally, patients in Texas in 2013 travelled a mean distance of 15 miles (24 km) to reach an abortion facility. The mean distance increased by 20 miles (32 km), to 35 miles (56 km), in 2014 after the law came into effect,

Exhibit 6

Research in context

Evidence before this study

Between Feb 1, 2017, and April 1, 2017, we searched Google Scholar for studies about spatial inequality in abortion access using the search terms "abortion and distance", "abortion access", and "spatial inequality". We reviewed the reference lists and reverse citations of relevant articles. Studies of high-income countries in which abortion is legal have identified spatial disparities in access to abortion facilities. Within the USA, studies using data from individual states have shown an inverse association between distance to nearest abortion provider and county abortion incidence. Meanwhile, many areas of the USA are implementing restrictive policies aimed at curtailing abortion. However, no national study has examined spatial inequality in access to abortion in the USA.

Added value of this study

We present the first national estimates of spatial disparities in distance to the nearest abortion provider in the USA. This study is also the first to take into account the geographical distribution of women. This approach allowed estimation of the median distance that a woman would have to travel to an abortion provider in each county and state and the 80th percentile distance that 20% of women in each state live from the nearest clinic. We characterised spatial disparities within and across states, and the stability of these disparities over a 15 year period, from 2000 to 2014.

Implications of all the available evidence

We showed persistant spatial disparities in women's access to abortion in the USA that might be applicable to women in other high-income countries.

and the number of patients who travelled more than 50 miles (80 km) increased from 10% to 44%.[16]

A limitation of those analyses was that they examined users of abortion services and did not capture women who wanted abortions but did not make it to the clinic because of distance; thus, they did not fully capture spatial inequality in access to abortions.[4–7] Two studies[4,7] found that the number of abortions in a county in Texas decreased as the distance to the nearest abortion facility increased between 2012 and 2014. Previous studies[5,6] that used abortion data for the states of New York and Georgia in the 1970s also found that the further women lived from a county or state where abortion care was provided, the lower the abortion incidence. These studies suggest that distance has been a persistent barrier to abortion.

Between 2011 and 2014, abortion incidence in the USA decreased by 14% to 14·6 abortions per 1000 women (15–44 years) each year.[17] During the same period, the number of clinics providing abortions decreased by 6%, from 839 to 788, compared with a 1% decline across the preceding 3 year period.[17] The decline in clinics was greatest in the midwest (22%) and southern (13%) regions, which also had the highest number of abortion restrictions enacted over this period.[17] As abortion clinics closed and service availability shifted, women might have had to travel further to have an abortion.

Using abortion-clinic data for 2014, 2011, and 2000, we examined spatial disparities in distance to the nearest abortion clinic by state and county. Because a decline in the number of abortion clinics might have increased the distance women had to travel to reach a provider,[17] we also examined state-specific and county-specific changes in distance to abortion clinics between 2011 and 2014. In a supplementary analysis to assess the long-term stability of access to abortion, we also analysed change since 2000.

Methods

Study design

We obtained the location of all abortion clinics in the USA from the Guttmacher Institute's Abortion Provider Census (APC). Since 1973, the Guttmacher Institute has regularly surveyed all known abortion-providing facilities to collect information about number of abortions and other aspects of service provision. The APC provides the most accurate counts of abortion available in the USA.[18] In the most recent APC, information was collected for 2014.[17] We also used data for 2011 and 2000 in this analysis. Approval for the study was obtained through expedited review by the Guttmacher Institute's federally registered institutional review board.

To identify clinics providing abortion services to the public, we limited the analysis to facilities that had caseloads of 400 abortions or more per year and those affiliated with Planned Parenthood that did at least one abortion in the period of interest. We included Planned Parenthood facilities that provided fewer than 400 abortions in a year because of name recognition and because their websites indicated whether they provided abortion services. These providers did 95% of all abortions in 2014; of the remainder, 2·1% occurred in hospitals, 1·4% in private physicians' offices, and 1·5% in health clinics.

Not all locations where abortions are done are accessible and discoverable to a woman seeking abortion care. Abortion providers in the USA have been targets of domestic terrorism, and doctors might be unable to maintain a practice if they are known to be willing to do abortions. Our data collection efforts showed that facilities doing small numbers of abortions seldom advertise their services. Thus, it is possible for a woman to live near to an abortion provider without knowing of that physician or that the physician provides abortions. Such a provider would not constitute a public point of access, and these were excluded from our analysis.

Moreover, confidentiality concerns did not allow us to reveal the locations of low-volume providers because doing so would threaten their safety.

Statistical analysis

To measure the distance between women and abortion providers, we first needed to specify the location of both. For women, we used the smallest publicly available geographical units, census block groups, which are geographical subdivisions of census tracts.[19] For their coordinates, we used population-weighted centroids.[20] For abortion providers, we geocoded (ie, determined the latitude and longitude of) each provider using Maptitude 2016, and linked each census block group to the nearest provider. Some women obtain abortions outside their state of residence; as such, in our analysis the nearest provider could be in another county or state. We used Open Source Routing Machine 4.9 to compute driving distance.[21]

	2011		2014		Change in distance, 2011–14	
	Median	80th percentile	Median	80th percentile	Median	80th percentile
USA	10·59 (17·04)	40·26 (64·80)	10·79 (17·36)	42·54 (68·46)	0·20 (0·32)	2·28 (3·66)
Northeast						
Connecticut	5·74 (9·24)	10·65 (17·13)	5·17 (8·32)	9·70 (15·60)	−0·57 (−0·92)	−0·95 (−1·53)
Maine	46·12 (74·22)	129·73 (208·77)	25·31 (40·73)	40·36 (64·95)	−20·81 (−33·49)	−89·37 (−143·82)
Massachusetts	9·67 (15·56)	21·64 (34·82)	9·77 (15·72)	21·52 (34·63)	0·10 (0·16)	−0·12 (−0·19)
New Hampshire	15·08 (24·27)	24·28 (39·07)	14·98 (24·10)	24·14 (38·84)	−0·10 (−0·16)	−0·14 (−0·23)
New Jersey	6·70 (10·78)	14·37 (23·12)	5·43 (8·74)	11·65 (18·75)	−1·27 (−2·04)	−2·72 (−4·37)
New York	3·19 (5·14)	9·66 (15·55)	3·17 (5·10)	9·12 (14·67)	0·03 (−0·04)	−0·54 (−0·87)
Pennsylvania	12·96 (20·86)	51·92 (83·55)	13·00 (20·91)	50·92 (81·95)	0·04 (0·06)	−0·99 (−1·60)
Rhode Island	7·07 (11·38)	18·90 (30·41)	7·07 (11·38)	18·83 (30·31)	0·00 (0·00)	−0·07 (−0·11)
Vermont	18·86 (30·36)	34·98 (56·29)	15·78 (25·40)	34·08 (54·84)	−3·08 (−4·96)	−0·90 (−1·45)
Midwest						
Illinois	9·96 (16·03)	29·56 (47·57)	10·41 (16·75)	32·67 (52·58)	0·45 (0·72)	3·11 (5·01)
Indiana	21·34 (34·34)	60·51 (97·37)	21·32 (34·31)	60·30 (97·04)	−0·02 (−0·03)	−0·21 (−0·34)
Iowa	17·61 (28·33)	47·76 (76·87)	12·16 (19·57)	47·92 (77·12)	−5·45 (−8·77)	0·16 (0·25)
Kansas	105·58 (169·92)	188·93 (304·05)	32·04 (51·57)	100·50 (161·74)	−73·54 (−118·35)	−88·43 (−142·31)
Michigan	10·92 (17·57)	35·35 (56·89)	12·63 (20·33)	42·85 (68·96)	1·71 (2·76)	7·50 (12·07)
Minnesota	16·47 (26·50)	60·43 (97·25)	17·77 (28·59)	60·55 (97·44)	1·30 (2·09)	0·12 (0·20)
Missouri	29·54 (47·54)	97·62 (157·10)	36·99 (59·53)	124·38 (200·17)	7·45 (11·99)	26·76 (43·07)
Nebraska	9·21 (14·82)	97·16 (156·36)	9·36 (15·06)	98·13 (157·92)	0·15 (0·24)	0·97 (1·56)
North Dakota	137·13 (220·68)	284·23 (457·42)	151·58 (243·94)	286·78 (461·52)	14·46 (23·27)	2·55 (4·11)
Ohio	16·43 (26·44)	45·26 (72·83)	15·41 (24·80)	45·58 (73·36)	−1·02 (−1·64)	0·33 (0·53)
South Dakota	95·87 (154·29)	327·33 (526·79)	92·06 (148·16)	329·85 (530·83)	−3·81 (−6·14)	2·51 (4·04)
Wisconsin	29·18 (46·96)	66·82 (107·53)	29·53 (47·53)	64·78 (104·25)	0·35 (0·56)	−2·04 (−3·28)
South						
Alabama	26·59 (42·80)	60·91 (98·03)	26·20 (42·16)	60·01 (96·58)	−0·40 (−0·64)	−0·90 (−1·45)
Arkansas	49·29 (79·32)	82·10 (132·13)	48·35 (77·81)	81·63 (131·36)	−0·94 (−1·51)	−0·47 (−0·76)
Delaware	6·65 (10·71)	19·36 (31·15)	6·68 (10·75)	19·39 (31·20)	0·03 (0·04)	0·03 (0·05)
Florida	8·34 (13·42)	22·58 (36·33)	7·84 (12·62)	20·74 (33·38)	−0·50 (−0·80)	−1·84 (−2·95)
Georgia	20·11 (32·37)	63·05 (101·47)	17·95 (28·89)	59·94 (96·46)	−2·16 (−3·48)	−3·11 (−5·01)
Kentucky	38·88 (62·57)	91·24 (146·83)	38·18 (61·45)	90·51 (145·66)	−0·70 (−1·13)	−0·73 (−1·17)
Louisiana	34·39 (55·34)	75·34 (121·24)	35·06 (56·42)	84·81 (136·48)	0·67 (1·07)	9·47 (15·24)
Maryland	5·86 (9·42)	15·53 (24·99)	6·20 (9·97)	16·61 (26·73)	0·34 (0·55)	1·08 (1·74)
Mississippi	68·31 (109·94)	95·30 (153·37)	68·80 (110·72)	94·92 (152·76)	0·49 (0·78)	−0·38 (−0·61)
North Carolina	19·07 (30·69)	46·41 (74·68)	18·34 (29·52)	45·68 (73·52)	−0·73 (−1·17)	−0·72 (−1·16)
Oklahoma	21·47 (34·55)	75·59 (121·65)	20·79 (33·46)	75·09 (120·84)	−0·68 (−1·09)	−0·50 (−0·81)
South Carolina	24·24 (39·01)	52·05 (83·76)	23·98 (38·59)	51·71 (83·23)	−0·26 (−0·42)	−0·33 (−0·54)
Tennessee	26·99 (43·43)	68·50 (110·23)	26·91 (43·31)	68·54 (110·30)	−0·08 (−0·13)	0·04 (0·06)
Texas	14·01 (22·55)	32·86 (52·88)	17·23 (27·72)	89·36 (143·81)	3·22 (5·18)	56·50 (90·93)
Virginia	10·91 (17·56)	40·22 (64·73)	11·25 (18·10)	39·67 (63·85)	0·34 (0·54)	−0·55 (−0·88)
West Virginia	59·94 (96·46)	91·46 (147·18)	59·81 (96·25)	91·44 (147·15)	−0·13 (−0·21)	−0·02 (0·04)

(Table continues on next page)

	2011		2014		Change in distance, 2011–14	
	Median	80th percentile	Median	80th percentile	Median	80th percentile
(Continued from previous page)						
West						
Alaska	9·31 (14·99)	156·24 (251·45)	9·31 (14·98)	154·26 (248·26)	0·00 (0·00)	−1·99 (−3·20)
Arizona	8·13 (13·08)	20·94 (33·69)	11·71 (18·84)	31·80 (51·18)	3·58 (5·76)	10·87 (17·49)
California	4·51 (7·26)	10·85 (17·47)	4·50 (7·24)	10·95 (17·63)	−0·01 (−0·02)	0·10 (0·16)
Colorado	10·26 (16·51)	25·73 (41·41)	9·73 (15·66)	20·08 (32·32)	−0·53 (−0·85)	−5·65 (−9·09)
Hawaii	14·00 (22·54)	29·97 (48·24)	14·00 (22·54)	30·20 (48·61)	0·00 (0·00)	0·23 (0·37)
Idaho	26·79 (43·12)	118·29 (190·37)	24·65 (39·67)	115·81 (186·37)	−2·14 (−3·45)	−2·48 (−4·00)
Montana	27·82 (44·76)	113·39 (182·48)	74·02 (119·13)	123·83 (199·29)	46·21 (74·37)	10·45 (16·81)
Nevada	7·22 (11·62)	13·26 (21·33)	7·10 (11·43)	12·06 (19·41)	−0·12 (−0·19)	−1·19 (−1·92)
New Mexico	27·27 (43·89)	102·09 (164·29)	26·52 (42·67)	112·45 (180·96)	−0·75 (−1·21)	10·36 (16·67)
Oregon	8·07 (12·99)	36·05 (58·02)	8·16 (13·12)	35·77 (57·56)	0·08 (0·13)	−0·29 (−0·46)
Utah	29·51 (47·49)	53·62 (86·29)	29·35 (47·23)	50·97 (82·03)	−0·16 (−0·26)	−2·65 (−4·26)
Washington	6·11 (9·84)	16·53 (26·61)	6·36 (10·24)	15·25 (24·55)	0·25 (0·40)	−1·28 (−2·06)
Wyoming	168·36 (270·95)	273·04 (439·42)	168·49 (271·16)	275·01 (442·59)	0·13 (0·21)	1·97 (3·17)

Data are miles (km).

Table: **Median and 80th percentile distances to nearest abortion clinic for women aged 15–44 years in 2011–14, by state**

To estimate mean and percentile distances for each state and county, we weighted each block group by the approximate number of women of reproductive age (15–44 years). We obtained population data for 2000 and 2010 from the Decennial Census.[22,23] The smallest geographical area for which age and sex distributions were available was census tract; therefore, we multiplied each block group's population by the proportion of the census tract that was made up of women aged 15–44 years. To account for population growth after 2010, the last year a census was done, we scaled each block group's population using the Census Bureau's 2011 and 2014 county population estimates.[24]

Mean distances were right skewed by the small proportion of women who lived several 100 miles from the nearest provider. For this reason, we used median distance or the value for which half of women in a county lived from the nearest provider. In our state-level analyses, we also examined 80th percentile distances.

We analysed whether distance to provider varied by the National Center for Health Statistics' urban-rural classification scheme, an extension of the Office of Management and Budget metropolitan statistical area (MSA) classification.[25]

No smooth gradient was seen in the number of abortions done by providers; of the providers excluded from the analysis in 2014, 631 (62%) did fewer than 25 abortions, whereas 38 (4%) did 300–399 abortions. A concern was that a small number of abortions might have placed a provider above or below 400 abortions so as to substantively affect our results. To address this possibility, we did a sensitivity analysis that included all providers who did at least 200 abortions.

Another concern was that rural areas might have been served by providers who did very few abortions. However, although 43% of counties were rural, less than 1% of the excluded providers were in rural areas. All of these were either hospitals or physicians' offices, except for one clinic, which did not advertise abortion services on its website.

We excluded the District of Columbia from the tables and discussion of the findings (but not from the overall analysis) because it is not a state. In both 2011 and 2014, the District of Columbia had four or more abortion clinics,[17,26] and residents would have had to travel a median distance of 2 miles to reach the nearest clinic (shorter than the median distance in any state).

Role of the funding source

The funding source did not have any role in the study design, data collection, data analysis, writing of the manuscript, or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Nationally, half of all women of reproductive age in 2014 lived within 10·79 miles (17·36 km) of an abortion clinic (table). The median distance a woman would have had to travel to reach the nearest abortion clinic in 2014 was less than 15 miles (24 km) in 23 (46%) states (figure 1 and table). These states were located in all four geographical regions. Because we considered the concentration of residents in census block groups, many women in states with large rural populations would not have had to travel far to reach a clinic. For example, although a third of residents in Alaska live in rural areas,[27] we found that half

of all women in this state lived within 9·31 miles (14·98 km) of the nearest abortion clinic.

The median distance to the nearest clinic providing abortion services in 2014 was 15–29 miles (24–47 km) in 16 (32%) states and 30–89 miles (48–143 km) in eight (16%) states. At least half of all women in three (6%) states, including Wyoming (168·49 miles [271·16 km]), North Dakota (151·58 miles [243·94 km]), and South Dakota (92·06 miles [148·16 km]), would have had to travel more than 90 miles (145 km) to reach the nearest clinic.

The median state distances concealed sizable minorities of women who would have had to travel substantial distances to reach an abortion provider. For example, compared with the median distance of 9·31 miles (14·98 km) in Alaska, the 80th percentile distance showed that 20% of women in Alaska would have had to travel at least 154·26 miles (248·26 km) to reach the nearest abortion clinic in 2014 (table). In 26 (52%) states, at least 20% of women would have had to travel more than 50 miles (80 km) to reach the nearest facility providing abortion care.

Examining distance to the nearest clinic by county provided a more complex picture (figure 2). Substantially more variation was seen between counties than between states, and women in many counties had to travel considerably further than their state median distance. However, even in states such as Texas, in which most of the landmass was far from an abortion clinic, most women lived reasonably close to an abortion clinic because of the concentration of both women and clinics in urban areas (appendix).

Counties where women would have had to travel 180 miles (290 km) or more to reach the nearest clinic were concentrated in the middle of the country, covering large portions of Montana, Wyoming, North Dakota, South Dakota, Nebraska, Kansas, and Texas. There were also areas with large travel distances in some states bordering Canada (Minnesota and Michigan), as well as pockets in California, Nevada, Utah, Idaho, and Missouri. Although geographically sizable, most of these areas were not densely populated and were generally rural (appendix). However, several of them were located in or near to medium or small metropolitan areas, the largest of which were located in Texas: Corpus Christi (324000 residents), Lubbock (246000), Amarillo (199000), and Brownsville (183000).

Between 2011 and 2014, the median distance a woman would have had to travel to reach an abortion clinic decreased in nine [18%] states; remained stable, changing no more than 1 mile (1·6 km) in 34 (68%) states; and increased in seven [14%] states (table). Most of the changes in distance to the nearest clinic were 5 miles (8 km) or less. The exceptions were Kansas (73·54 miles [118·35 km]) and Maine (20·81 miles [33·49 km]), where the median distance decreased, and Montana (46·21 miles [74·37 km]), North Dakota (14·46 miles [23·27 km]), and Missouri (7·45 miles [11·99 km]), where the median distance increased.

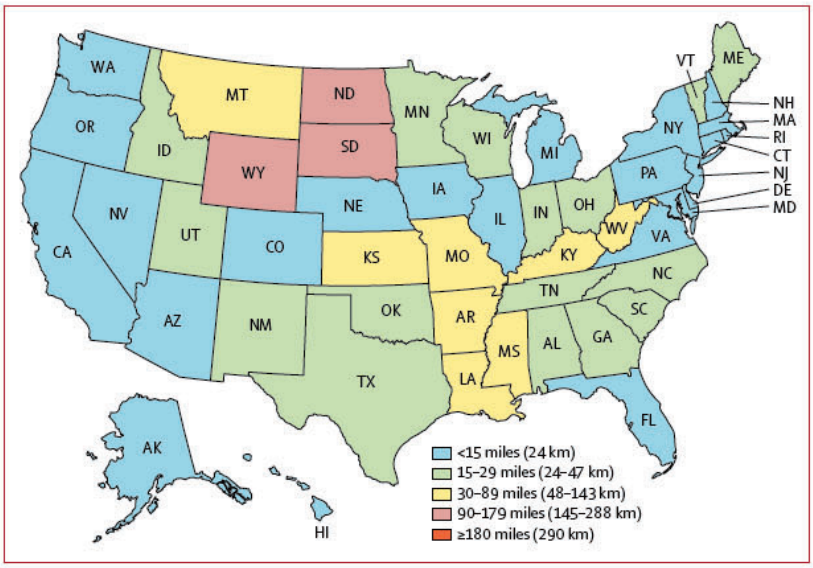

Figure 1: **Median distance to the nearest abortion provider by state, 2014**
Alaska and Hawaii are inset in the bottom-left corner.

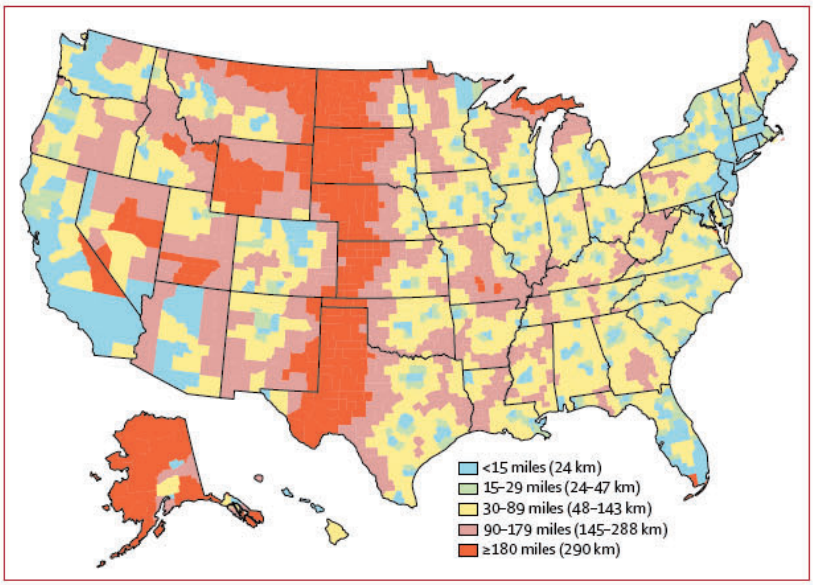

Figure 2: **Median distance to the nearest abortion provider by county, 2014**
Alaska and Hawaii are inset in the bottom-left corner.

See Online for appendix

Similarly, little to no change was seen in the median distance to the nearest clinic in most counties (figure 3). Counties where the median distance to the nearest provider increased by 30 miles (48 km) or more were especially prominent in Texas, Iowa, Montana, and Missouri, and were present only outside large metropolitan areas (appendix). Texas and Missouri also had the largest increases in the 80th percentile distance that 20% of women would have had to travel to reach a clinic (56·50 miles [90·93 km] for Texas and 26·76 miles

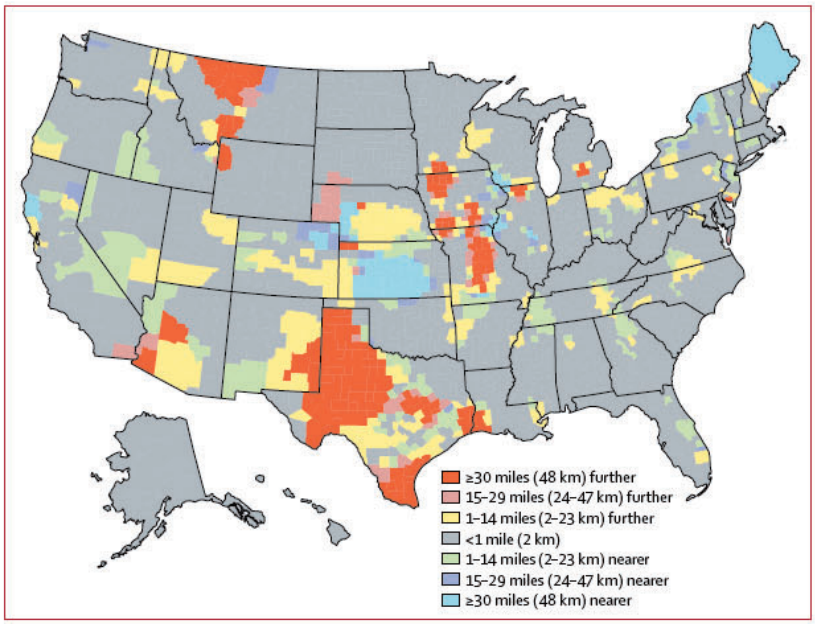

Figure 3: **Change in median distance to the nearest abortion provider by county, 2011–14**
Alaska and Hawaii are inset in the bottom-left corner.

[43·07 km] for Missouri). Conversely, the 80th percentile distance increased by less than 1 mile in Iowa, and the median distance actually decreased by 5·45 miles (8·77 km) in this state (table). Although counties where the median distance to the nearest provider increased by 30 miles (48 km) or more were located in all four geographical regions, New Jersey was the only state in the northeast to show this degree of change. Counties where the median distance to a clinic increased by 15–29 miles (24–47 km) were more sparse than those where the median distance to the nearest provider increased by 30 miles (48 km) or more, although they too were not found in large metropolitan areas (appendix). These counties were also scattered across all four regions, although only one state in the northeast, Virginia, experienced this level of decline in access.

Counties where the median distance to the nearest clinic decreased by more than 30 miles (48 km) were most commonly in the midwest, occurring in Illinois, Iowa, Kansas, Missouri, Nebraska, and Wisconsin. Distance to the nearest clinic also decreased by 30 miles (48 km) or more in counties in California and Colorado (in the west) and in Maine and upstate New York (in the northeast).

Our findings showed spatial disparities that were broadly unchanged in the period of 2011–14, despite several abortion restrictions being enacted during this period. We confirmed the consistency of the spatial disparities in our supplemental analysis of data from 2000. These spatial disparities have persisted for at least 15 years (appendix).

To assess the robustness of our results, we did a sensitivity analysis with inclusion of providers who did 200–399 abortions each year. State distances in 2014 were almost identical to those from the original primary analysis, with one exception: in Texas, the 80th percentile distance increased by 30 miles (48 km) because of a restrictive law that forced clinic closures (appendix).

Discussion

To our knowledge, this study is the first to provide national estimates of spatial disparity in distance to the nearest abortion clinic for all women aged 15–44 years in the USA. Research has shown that living far from a provider can make abortion inaccessible.[4–6] Travelling long distances can impose a substantial burden on women with respect to transportation costs, travel duration, time off work, and arrangement of childcare, particularly for women who are economically disadvantaged. However, distance can be contextualised within several factors that can affect access to abortion care. The presence of one nearby clinic does not necessarily show that the clinic meets the needs of all prospective patients, that it is open daily, or that it has the capacity to meet demand.[28] Numerous barriers to access can have compounding effects on a woman's ability to access care. For example, in 2014, 11 US states (an increase from nine states in 2011) required that a woman have in-person counselling, followed by waiting for 24–72 h, before obtaining an abortion (appendix). For these women, even seemingly short distances of 30 miles (48 km) can pose a substantial barrier to care because they would have to travel to and from the clinic twice (120 miles [193 km] in total).

Almost all patients who have an abortion in the USA are economically disadvantaged, and many either do not have health insurance or are unable to use insurance to pay for the procedure.[8] These women might be able to travel to an abortion clinic, but they will be unable to access the service if they cannot afford to pay for the procedure. Distance might compound these cost barriers.

Most women would not have to travel considerable distances to reach an abortion clinic because almost all women and providers in the USA are in metropolitan areas. However, a sizable minority of women would have to travel 90 miles or more, and variation between counties is greater than between states. For example, in Alaska in 2014, half of all women lived 9·31 miles (14·98 km) or less from an abortion clinic, but a fifth of women lived 154·26 miles (248·26 km) or even further from a clinic; similar examples included Idaho, Montana, Nebraska, New Mexico, and Texas. Although half of all woman in the USA would have had to travel no more than 10·79 miles (17·36 km) to reach the nearest abortion clinic, 20% of women would have had to travel 42·54 miles (68·46 km) or more. Although policies are implemented at the state level, the consequences of restrictive legislation might not be felt equally across counties within a state; women in rural counties are likely to be most adversely affected by clinic closures.

Increases in distance in excess of 30 miles (48 km) between 2011 and 2014 were particularly evident in numerous counties in Texas, Missouri, Iowa, and Montana. All of these states, except for Iowa, adopted abortion restrictions during this period (appendix). These states were among those that had the largest proportionate decline in clinics.[17] A hostile environment might have contributed to clinic closures, meaning that more women would have had to travel further to access care in 2014 than in 2011. By contrast, Iowa enacted no major restrictions during the study period and was not considered hostile to abortion rights, although it had five fewer clinics in 2014 than in 2011 (appendix). Research has suggested that efforts to increase access to long-acting contraceptive methods in Iowa might have contributed to reductions in the number of abortions.[29] Reduced need for abortion services might have contributed to the decline in clinics and, in turn, the increase in distance that some women in some counties would have to travel for an abortion. The median distance to a clinic decreased by about 5 miles (8 km) for Iowa during the study period, suggesting that abortion services were redistributed and that women, particularly those living in metropolitan areas, would not have had to travel quite as far.

Texas was an outlier in that the distance that 20% of women would have had to travel increased by about 56 miles (90 km). This finding was probably due to an abortion restriction enacted in 2013 requiring that physicians who provide abortion care have admitting privileges at nearby hospitals. This law resulted in the closure of more than half of the abortion care facilities in the state between 2013 and 2014.[30] Our estimates of distance to nearest provider for women in Texas in 2014 are probably too low because they were calculated with inclusion of facilities that provided at least 400 abortions in 2014, several of which were closed at some point that year.[31] Although some of the more onerous restrictions were struck down by the Supreme Court in June, 2016, most clinics have not yet reopened,[4] and the distance to the nearest provider has probably not improved.

The median distance to the nearest provider decreased by more than 20 miles (32 km) in Kansas and Maine. A new clinic opened in Kansas, and two clinics in Maine had increased caseloads so that they provided 400 or more abortions in 2014. These findings suggested that abortion might have become more accessible for women in these states.

This study had several limitations. First, there are numerous barriers to abortion access in the USA, and distance is not the only obstacle. Abortion restrictions, stigma, and financial constraints could prevent a woman from having an abortion, regardless of distance. Second, our estimates might be conservative because they do not capture the effect of mandated counselling and waiting periods, which might force women to make multiple trips to an abortion clinic. Third, a woman might not visit the closest abortion provider to her home; for example, the closest provider might not offer the necessary or desired services. Fourth, our analysis did not capture women's qualitative experiences. Fifth, the inclusion criteria might have affected the measured distances, but modifying these criteria would have led to inclusion of locations that were not public points of access. Finally, although we documented spatial disparities, it was beyond the scope of our analysis to fully address their causal determinants (eg, reduced demand for services might have affected a clinic's ability to support itself).

In conclusion, abortion is an important component of reproductive health, and restricting access to abortions can lead to them being done later or under potentially unsafe conditions. Our analysis showed substantial and persistent spatial disparities in access to abortion. Enacting restrictions at the state level is a stated priority of many policy makers.[32] Such efforts, if successful, could not only reduce access to abortion, especially for economically disadvantaged women who might not have the resources to overcome obstacles posed by travel, but could potentially exacerbate existing spatial inequality.

Contributors

JMB led the conceptualisation of the research and analysis of data. RKJ led the Abortion Provider Censuses and contributed to conceptualisation of the research. KLB contributed to data collection, geocoded the data, and co-led the analysis, under the supervision of JMB and RKJ. All authors contributed to interpretation of the results and writing of this report.

Declaration of interests

We declare no competing interests.

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Exhibit 7

OPEN

Original Research

Medication Abortion With Pharmacist Dispensing of Mifepristone

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OBJECTIVE: To estimate effectiveness and acceptability of medication abortion with mifepristone dispensed by pharmacists.

METHODS: We conducted a prospective cohort study at eight clinical sites and pharmacies in California and Washington State from July 2018 to March 2020. Pharmacists at participating pharmacies underwent a 1-hour training on medication abortion. We approached patients who had already been evaluated, counseled, and consented for medication abortion per standard of care. Patients interested in study participation gave consent, and the clinician electronically sent a prescription to the pharmacy for mifepristone 200 mg orally, followed 24–48 hours later by misoprostol 800 micrograms buccally. Participants were sent web-based surveys about their experience and outcomes on days 2 and 14 after enrollment and had routine follow-up with study sites. We extracted demographic and clinical data, including abortion outcome and adverse events, from medical records. We performed multivariable logistic regression to assess the association of pharmacy experience and other covariates with satisfaction.

RESULTS: We enrolled 266 participants and obtained clinical outcome information for 262 (98.5%), of whom two reported not taking either medication. Of the 260 participants with abortion outcome information, 252 (96.9%) and 237 (91.2%) completed day 2 and 14 surveys, respectively. Complete medication abortion (primary outcome) occurred for 243 participants (93.5%, 95% CI 89.7–96.1%). Four participants (1.5%, 95% CI 0.4–3.9%) had an adverse event, none of which was serious or related to pharmacist dispensing. In the day 2 survey, 91.3% (95% CI 87.1–94.4%) of participants reported satisfaction with the pharmacy experience. In the day 14 survey, 84.4% (95% CI 79.1–88.8%) reported satisfaction with the medication abortion experience. Those reporting being very satisfied with the pharmacy experience had higher odds of reporting overall satisfaction with medication abortion (adjusted odds ratio 2.96, 95% CI 1.38–6.32).

CONCLUSION: Pharmacist dispensing of mifepristone for medication abortion is effective and acceptable to patients, with a low prevalence of adverse events.

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Each author has confirmed compliance with the journal's requirements for authorship.

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Dr. Grossman has served as a consultant to Planned Parenthood Federation of America and the Center for Reproductive Rights. Dr. Creinin and Dr. Meckstroth are consultants for Danco, Inc., the manufacturer of Mifeprex (mifepristone 200 mg). Dr. Rafie is a consultant for GenBioPro, the manufacturer of generic mifepristone. The other authors did not report any potential conflicts of interest.

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Medication abortion with mifepristone and misoprostol is approved by the U.S. Food and Drug Administration (FDA) for use through 70 days of gestation. Extensive research has documented the safety and effectiveness of medication abortion, as well as high levels of patient satisfaction.[1] Since mifepristone's approval in 2000, the FDA has required that the drug only be dispensed in clinics, medical offices, or hospitals, a restriction that is codified in the mifepristone Risk Evaluation and Mitigation Strategy.[2] The FDA instituted these restrictions likely because of the limited experience with medication abortion in the United States in 2000. However, there is no evidence that in-person dispensing improves safety, and medications associated with more risks to the patient do not have similar restrictions.[3]

Twenty years later, such evidence is still lacking, and countries such as Australia and Canada have approved mifepristone without dispensing restrictions.[4,5] The mifepristone Risk Evaluation and Mitigation Strategy may be a barrier to access; a national survey of obstetrician–gynecologists found that the number who would provide medication abortion might double if this dispensing restriction were removed.[6] The American College of Obstetricians and Gynecologists advocates the removal of the mifepristone Risk Evaluation and Mitigation Strategy.[7]

Pharmacists dispense medications and controlled substances for all types of indications, including sensitive health issues such as sexually transmitted infections and erectile dysfunction. Currently, 12 states permit pharmacists to prescribe hormonal contraception[8]; a recent national survey found that 65% of all pharmacists were interested in such prescribing.[9]

We performed this study under an FDA Investigational New Drug application to document clinical outcomes with and the acceptability of medication abortion when mifepristone is prescribed by clinicians and dispensed by pharmacists. We also sought to identify factors associated with satisfaction with the pharmacist-dispensing model, as well as to explore whether satisfaction with the pharmacy experience was associated with overall satisfaction with medication abortion.

METHODS

We performed a multicenter prospective cohort study of patients undergoing medication abortion who agreed to obtain pharmacist-dispensed mifepristone. The Institutional Review Boards (IRBs) of the University of California San Francisco (UCSF), Kaiser Permanente Northern California, and the University of Washington approved the study, with reliance on the University of California San Francisco IRB granted by the IRBs of the University of California, Davis, and the University of California, San Diego.

From July 2018 through March 2020, we enrolled patients at eight study sites in California and Washington State, each of which was paired with a nearby pharmacy that agreed to dispense mifepristone. Each of the clinical sites provided medication abortion before the study with clinic dispensing of mifepristone; patients obtained other prescribed medications at pharmacies. Six of the eight clinics partnered with an affiliated pharmacy in the same or adjacent building (n=5) or 1.5 miles away (n=1). Two clinics partnered with independent pharmacies, one of which was located in an adjacent building, and the other was located 1.5 miles away. Study investigators trained participating pharmacists on medication abortion and mifepristone dispensing using a standardized 1-hour presentation at the beginning of the study and as needed when new participating pharmacists were hired. At all study pharmacies, leadership permitted pharmacists to participate in the study if interested, including undergoing training, and committed to having coverage during study recruitment times by a pharmacist who could dispense mifepristone. Of note, three chain pharmacies near potential clinic sites declined to participate. Each clinical site principal investigator completed the mifepristone Prescriber Agreement Form.

Clinicians included physicians, physician assistants, and nurse practitioners. Research staff provided study details, including study coverage of clinical costs (see below) to patients only after the clinician had completed all medically necessary requirements for medication abortion. All patients approached for the study had already been fully evaluated for medication abortion medical eligibility according to the FDA-approved mifepristone labeling and local standard of care, signed the mifepristone Patient Agreement Form and any clinic-specific consent form, and received mifepristone use and follow-up instructions. Clinical follow-up options were site-specific and included returning for an in-clinic ultrasonography examination approximately 1–2 weeks later, obtaining serum human chorionic gonadotropin measurements on the day of taking mifepristone and 1–2 weeks later, or performing telephone follow-up 1 week later with a home urine pregnancy test 4 weeks after mifepristone.

Participants were eligible for the study if they spoke English or Spanish, were age 15 years or older (18 years or older at two study sites), had been fully evaluated and consented for medication abortion with a gestational age of 70 days or less confirmed by ultrasonography, and were willing to go to the study pharmacy to obtain mifepristone and to use misoprostol buccally per the FDA-approved mifepristone label. Participants also had to be willing and able to be contacted by email, telephone, or text message to complete survey data collection. Eligible and interested participants provided written study informed consent, including Health Insurance Portability and Accountability Act authorization to allow clinical data abstraction from their medical record.

A clinician then electronically prescribed mifepristone 200 mg and misoprostol 800 micrograms, along with analgesics, antibiotics, antiemetics, or contraceptives, as needed. The prescribing clinician instructed participants to use the mifepristone at an agreed-on time and take the misoprostol buccally 24–48 hours after swallowing the mifepristone, consistent with the FDA-approved labeling.[10] Participants went to the pharmacy to obtain the prescribed medications. A trained pharmacist dispensed the mifepristone and other prescribed medications, maintained a study log and provided brief counseling, unless declined by the patient.

On the day after enrollment, the University of California San Francisco study team emailed participants a link to a web-based survey (day 2 survey) in Qualtrics to collect sociodemographic information, including self-described race and ethnicity. Given the evidence of negative health care experiences during pregnancy among people of color due to racism,[11] we believed it was important to collect race and ethnicity information to explore associations with satisfaction outcomes. Participants also confirmed whether they obtained the medications at the pharmacy, and if and when they took or planned to take the medications. If they had taken the misoprostol, we asked the route of administration. If a participant obtained the medications and decided not to take them, we asked what they did or planned to do with the medications; if a participant reported they still had the medications, a survey prompt instructed them to return the medications to the pharmacy or the clinic. Participants were asked whether they thought the pregnancy had already been expelled and whether they had had a medical problem that required them to go to a hospital, emergency department, or doctor's office since starting the medication abortion, and, if so, we asked participants to provide details.

In addition, the day 2 survey assessed participant experiences obtaining mifepristone at the pharmacy with multiple choice questions as well as open-response fields for those who reported dissatisfaction to explain their responses. We asked whether the wait time at the pharmacy was "reasonable" or "too long." All participants were asked, "Did you feel that you got enough information from the pharmacist about how to use the medications?" with response options of "Yes," "No, I would have liked more information from the pharmacist," and "No, but I got all the information I needed from the doctor or nurse in clinic." We asked participants who reported having had a prior medication abortion, "How would you compare your experience of getting the abortion pill this time in the pharmacy compared with last time in the clinic?" with response options of "This time was better," "Last time was better," "They were both the same," or "Not sure."

Two weeks after enrollment, we sent participants an email link to the day 14 survey, which had similar questions about taking the medications, medical problems for which they sought care, follow-up with the clinic, use of additional misoprostol, and whether they thought the abortion was complete and reasons why they thought it was complete. If a participant reported being unsure whether the abortion was complete, a survey prompt instructed the participant to contact the clinical site and asked permission to follow-up with them again after the visit.

The day 14 survey also included questions about the patient's experience with the overall medication abortion experience and whether they would recommend medication abortion to a friend in a similar situation who decided to have an abortion. We also asked whether they would recommend that the friend "get the abortion pill at the pharmacy like you did." Finally, we asked, "If you have another medication abortion in the future, how would you feel about the way you get the service?" Responses options were "I would prefer to have medication abortion be available through many primary care providers and providers of women's health care (doctors and nurses) and I would like to pick up my abortion pill at the pharmacy," "I would prefer to have medication abortion available only in select clinics where the abortion pill can be given to me directly in clinic," "Either way is fine," or "Unsure." The day 14 survey also included open-response questions that allowed participants to elaborate on their responses.

Participants who did not complete the surveys were sent reminders by text, email, or phone, depending on their contact preferences. Those who had not

yet completed the day 2 survey received a longer day 14 survey, including the day 2 survey items. The surveys remained open for 1 month.

Six or more weeks after participants enrolled, site investigators abstracted data from patient charts and entered the de-identified data into an electronic REDCap form. Abstracted data included demographics, clinical information from the initial visit, and information about any follow-up visits or contacts with the patient related to the medication abortion, including whether the abortion was complete, additional treatments given, and adverse events. Adverse events were also identified from the patient surveys. Adverse events were captured up to 6 weeks after participants were recruited into the study, and any ongoing adverse events were followed until resolution. Adverse events were defined as serious using the FDA criteria and included death, hospitalization, blood transfusion, and surgery.[12,13]

Study participants received a $25 electronic gift card for completing each survey. Participants that had to travel from the clinic to the pharmacy also received a small stipend to cover travel expenses. The study covered the cost of mifepristone, misoprostol, and pharmacy dispensing fees, as well as the cost of other medications and clinical care related to the medication abortion provided during the initial and follow-up visits at some sites, depending on whether the site was able to bill for the service in the usual fashion or not.

We aimed to recruit a minimum of 300 and up to 350 patients for this study, which we thought was feasible during the study period. With a sample size of 300, if the proportion of patients with a complete abortion is 95%, the 95% CI of that proportion is ±3.1%; with a sample of 350, the interval is ±2.7%.

We examined four outcomes related to clinical experience and satisfaction with the pharmacist-dispensing model. These included two clinical outcomes: 1) effectiveness of medication abortion (primary outcome) and 2) adverse events, as well as two patient satisfaction outcomes that we examined in multivariate mixed-effects logistic regression analyses: 3) satisfaction with the pharmacy experience at day 2 and 4) satisfaction with the overall medication abortion experience at day 14. Effectiveness of medication abortion was defined as the proportion of participants who had a complete abortion with medications alone and did not undergo vacuum aspiration. Given the accuracy of patient self-assessment of abortion completion,[14,15] we used self-reported survey data to document abortion outcome if the participant did not have follow-up contact with the clinic. Satisfaction outcomes were based on participants' ratings on a Likert scale. On the day 2 survey, we asked participants "Overall, how satisfied were you with your experience at the pharmacy when you got the abortion pill?" with response options "Very satisfied," "Somewhat satisfied, "Somewhat dissatisfied," and "Very dissatisfied." On the day 14 survey we asked, "Looking back on your experience overall, how satisfied were you with the abortion pill?" with the same response options. We dichotomized responses to the two questions by those who were very satisfied compared with all other responses. We calculated 95% CIs using the binomial method.

We performed multivariable mixed-effects logistic regression analyses to explore associations between participant and pregnancy characteristics and our two patient satisfaction outcomes (satisfaction with pharmacy experience and satisfaction with overall medication abortion experience). We used mixed-effects regression with random intercepts for recruitment site to account for clustering. Independent variables included the following demographic and pregnancy characteristics, selected a priori based on our hypotheses and previous literature[16]: age, race and ethnicity, highest completed level of education, relationship status, parity, gestational age in days at the initial clinic visit, and prior abortion experience (none, previous medication abortion, or previous procedural abortion only). We also adjusted for whether the participant reported receiving adequate information from the pharmacist about medication abortion and pharmacy wait time (reasonable or too long). We included a dichotomized measure of satisfaction with treatment by pharmacy staff as an independent variable in the analysis of satisfaction with the pharmacy experience outcome. To assess whether the pharmacy experience contributed to overall satisfaction with the medication abortion experience, we also included satisfaction with the pharmacy experience as an independent variable to model this outcome.

To account for missing covariate data, we conducted multiple imputation then deletion methods, using chained equations.[17] We excluded participants with missing outcome data after performing multiple imputation. All demographic variables and pharmacy experience responses were collected from patient surveys except gestational age at the clinic visit, which came from clinical charts. Missing survey data for age, race and ethnicity, and parity were obtained from patients' clinical chart data when available.

We conducted all analyses using Stata 15 and reported significance at $P<.05$. Open-ended survey responses were sorted by relevance to study intervention and organized under unifying themes.

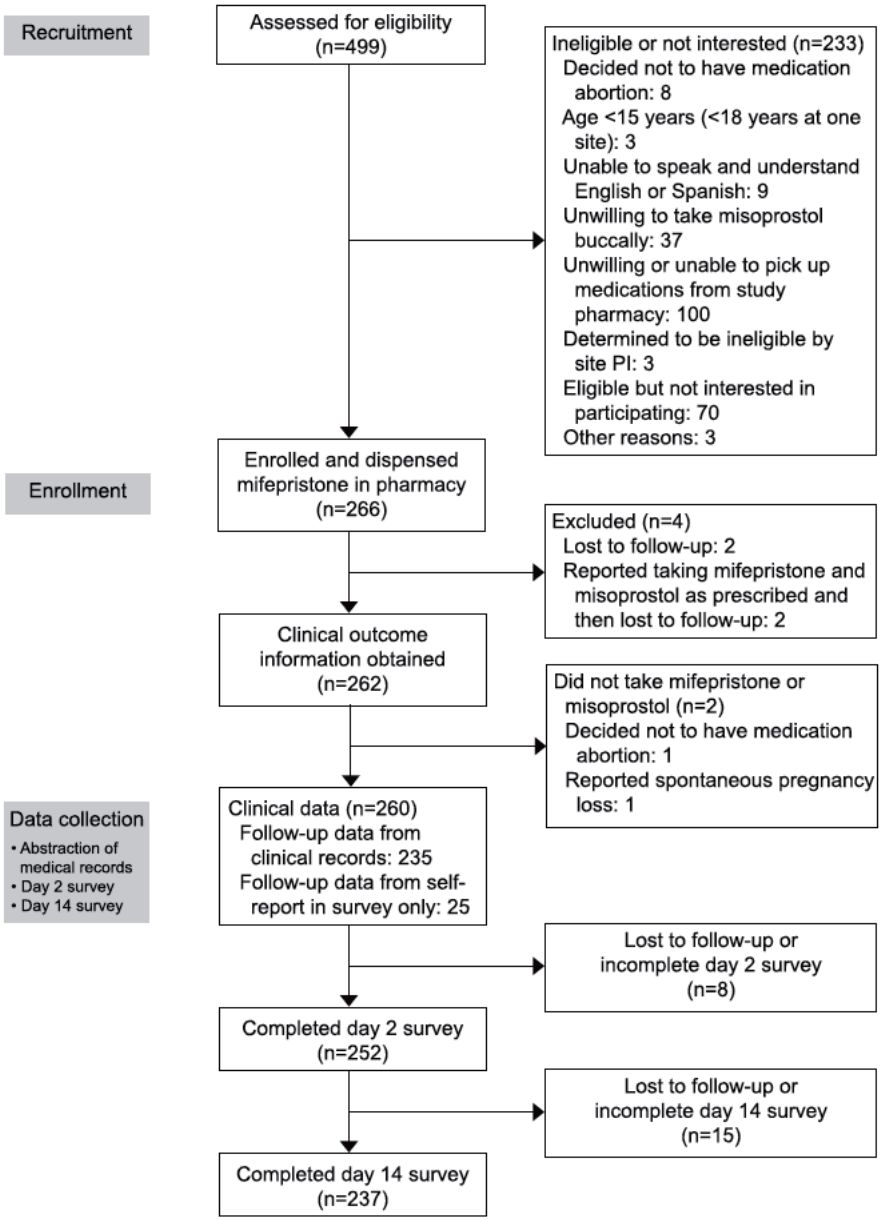

Fig. 1. Medication abortion study flow of patients who received mifepristone from pharmacists. PI, principal investigator.

Grossman. Pharmacist Dispensing of Mifepristone. Obstet Gynecol 2021.

RESULTS

Study recruitment began in July 2018 and was halted before reaching our desired sample size in March 2020 owing to the coronavirus disease 2019 (COVID-19) pandemic, which limited the ability to have research staff in clinical facilities and lengthen patient visits for the purposes of research consent. Research staff assessed 499 patients for eligibility, of whom 233 were ineligible (n=163) or declined to participate (n=70) (Fig. 1). We enrolled 266 participants, all of whom received the study medications from the pharmacy. The median number of participants recruited at the eight sites was 27 (range 8–74). Medication abortion and study outcome information was available for 262 participants (98.5%); the other four were lost to follow-up. In addition, one participant opted not to have a medication abortion and returned the medications to the study site, and one reported flushing the medications down the toilet after having a spontaneous pregnancy loss. The characteristics of the 260 participants (97.7%) who took the medications and have abortion outcome data are presented in Table 1. The median gestational age was 46 days at the time of initial clinic visit. Two hundred forty-six participants (94.6%) reported the date they took mifepristone; all had a gestational age of 70 days or less on that date.

Table 1. Characteristics of Study Participants Having Medication Abortion and Receiving Mifepristone at a Pharmacy (n=260)

Characteristic	Value
Age (y)	28 (16 44)
16 20	22 (8.5)
21 24	45 (17.3)
25 29	78 (30.0)
30 34	69 (26.5)
35 44	46 (17.7)
Race and ethnicity	
Non Hispanic White	99 (38.1)
Non Hispanic Black	29 (11.2)
Hispanic	65 (25.0)
Asian or Pacific Islander	45 (17.3)
Alaska Native or Native American	2 (0.8)
Other* and mixed race and ethnicity	19 (7.3)
Missing	1 (0.4)
Education	
High school or less	39 (15.0)
Some college or professional school	93 (35.8)
College degree	90 (34.6)
Advanced degree	28 (10.8)
Missing	10 (3.8)
Relationship status	
Neither married nor in a relationship	84 (32.3)
Married	54 (20.8)
Committed relationship	110 (42.3)
Missing	12 (4.6)
Parity	
Nulliparous	171 (65.8)
Parous	89 (34.2)
History of abortion	
None	165 (63.5)
Previous medication abortion	48 (18.5)
Previous procedural abortion only	40 (15.4)
Missing	7 (2.7)
Gestational age at initial clinic visit (d)	46 (30 70)
49 or less	176 (67.7)
50 56	43 (16.5)
57 63	32 (12.3)
64 70	9 (3.5)

Data are median (range) or n (%).
* Four participants selected "other" race and did not give additional information.

Table 2. Acceptability and Satisfaction at Day 2 Survey Among Women Having Medication Abortion and Receiving Mifepristone at a Pharmacy (n=252)

	n (%)
Satisfaction with pharmacy experience	
Very satisfied	173 (68.7)
Somewhat satisfied	57 (22.6)
Somewhat dissatisfied	18 (7.1)
Very dissatisfied	4 (1.6)
Satisfaction with treatment by pharmacy staff	
Very satisfied	201 (79.8)
Somewhat satisfied	43 (17.1)
Somewhat dissatisfied	5 (2.0)
Very dissatisfied	3 (1.2)
Wait time at pharmacy	
Reasonable	200 (79.4)
Too long	51 (20.2)
Missing	1 (0.4)
Adequate information received from pharmacist	
No, I would have liked more information	4 (1.6)
No, but I got all the information I needed from the doctor or nurse	96 (38.1)
Yes	151 (59.9)
Missing	1 (0.4)
Current vs previous experience among those who had previous medication abortion (n=48)	
This time better	17 (35)
Last time better	1 (2)
Same	22 (46)
Not sure	8 (17)

We obtained abortion outcomes for most participants (n=235, 90.4%) based on completed clinical follow-up, with the remainder based on survey responses. Follow-up assessments are detailed in online Appendix 1, available online at http://links.lww.com/AOG/C227. Complete abortion occurred for 243 participants (93.5%, 95% CI 89.7–96.1%) with medication alone. Twenty-seven participants received a second dose of misoprostol, including 18 who ultimately had a complete abortion. Seventeen participants were diagnosed with incomplete abortion based on symptoms and ultrasonography findings, all of whom underwent vacuum aspiration. No participant had an ongoing pregnancy. Outcomes by gestational age are presented in Appendix 2, available online at http://links.lww.com/AOG/C227.

Four participants (1.5%, 95% CI 0.4–3.9%) had an adverse event possibly related to the abortion. Three participants went to an emergency department: one received intravenous fluids for dehydration, one reported heavy bleeding and was treated with pain medication, and one was diagnosed with pelvic inflammatory disease after an aspiration for incomplete abortion. None were hospitalized. In addition, one participant reported at a follow-up visit that she had transient pain and swelling in her cheeks after taking the misoprostol buccally, which had resolved and was thought to be a possible allergic reaction. After review by the site principal investigators, no adverse event was thought to be related to pharmacist dispensing. No participant reported a serious adverse event, and none were identified in chart abstraction.

For survey data, we excluded 8 of 260 (3.1%) participants missing pharmacy satisfaction data and 23 of 260 (8.8%) participants missing overall medication abortion satisfaction data. Participants completed the day 2 survey a median of 2 days after enrollment (interquartile range 1–4 days) and completed the day 14 survey a median of 16 days after enrollment (interquartile range 14–21 days). Table 2 shows participants' satisfaction as reported in the day 2 survey (n=252). Among survey respondents, 91.3% (95% CI 87.1–94.4%) reported being very (68.7%) or somewhat (22.6%) satisfied with their experience at the pharmacy, and 96.8% (95% CI 93.8–98.6%) reported being very (79.8%) or somewhat (17.1%) satisfied with their treatment by pharmacy staff. Four-fifths (79.4%) of participants said the wait time in the pharmacy was reasonable.

Participants who were less than very satisfied with the pharmacy experience (n=76) or treatment by pharmacy staff (n=42) gave open-ended responses describing their dissatisfaction. Common themes cited included complaints about long wait times (n=38), confusion on the part of pharmacists or staff regarding dispensing (n=27), perceived negative pharmacist attitudes (n=10), inadequate pharmacist knowledge about the medications (n=8), initially not receiving all prescribed medications (n=8), and privacy not adequately maintained (n=4), among others. Some participants pointed to more than one factor that contributed to their dissatisfaction.

In the day 2 survey, most participants reported they received adequate information from the pharmacist (59.9%) or reported they did not receive enough information from the pharmacist but received all the information they needed from the clinician they had seen previously (38.1%). Only four participants (1.6%) reported that they would have liked more information about how to use the medications from the pharmacist.

Among the 48 participants who reported a prior medication abortion, most said the current experience was the same (n=22, 46%) or better (n=17, 35%) as receiving the medications in the clinic. Eight (17%) were unsure and one (2%) reported the experience as worse. In an open-response field, participants wrote they appreciated the ability to schedule when they would take the medications, which improved convenience and allowed them to have more control over when the abortion would take place. Although some participants saw this model of care as allowing more privacy and social support, a few thought the model was less private and felt less supported by the pharmacy staff compared with the clinic staff.

Table 3. Acceptability and Satisfaction at Day 14 Survey Among Women Having Medication Abortion and Receiving Mifepristone at a Pharmacy (n=237)

	n (%)
Overall satisfaction with medication abortion	
Very satisfied	155 (65.4)
Somewhat satisfied	45 (19.0)
Neither satisfied nor dissatisfied	23 (9.7)
Somewhat dissatisfied	12 (5.1)
Very dissatisfied	2 (0.8)
Would recommend medication abortion to friend	
Yes	161 (67.9)
No	14 (5.9)
Depends	53 (22.4)
Unsure	8 (3.4)
Missing	1 (0.4)
Would recommend pharmacy dispensing	
Yes	176 (74.3)
No	10 (4.2)
Depends	42 (17.7)
Unsure	9 (3.8)
Future model preference reported	
Prefer to have medication abortion available through primary care and pick up at pharmacy	147 (62.0)
Prefer to have medication abortion available only in select clinics where pill is given directly in clinic	13 (5.5)
Either way	68 (28.7)
Unsure	7 (3.0)
Missing	2 (0.8)

Table 3 shows measures of satisfaction collected from the 237 (91.2%) women who completed the day 14 survey. Overall, 84.4% (95% CI 79.1–88.8%) reported being very (65.4%) or somewhat (19.0%) satisfied with their medication abortion experience. The majority said they would recommend medication abortion (67.9%) and pharmacist dispensing (74.3%) to a friend in a similar situation. When asked how they would prefer to obtain medication abortion in the future, if needed, the majority (62.0%) said they would prefer to have medication abortion available through prescriptions from primary care clinics with medications dispensed in pharmacies. Only 5.5% said they would prefer to have the service only available in select clinics where the medications are dispensed directly to patients in clinic. About one quarter (28.7%) said either way was fine, and 3.0% were unsure.

Table 4 shows the results of multivariable mixed-effects logistic regression analyses exploring factors associated with patient satisfaction with the pharmacy and medication abortion experience. Those reporting

Table 4. Multivariable Adjusted Odds Ratios for Reporting Satisfaction With the Pharmacy Experience and Overall Abortion Experience Among Women Having Medication Abortion and Receiving Mifepristone at a Pharmacy

	Very Satisfied With Pharmacy Experience at Day 2 Survey (n=252)		Very Satisfied With Medication Abortion Experience Overall at Day 14 Survey (n=237)	
Participant Characteristics	aOR (95% CI)	%	aOR (95% CI)	%
Received adequate information from pharmacist				
No or No, but received the info from clinician	Ref	64.0	Ref	55.2
Received adequate info from the pharmacy	1.86 (0.82 4.26)	71.5	1.86 (0.99 3.51)	72.1
Wait time at pharmacy				
Reasonable wait time	Ref	81.0	Ref	68.5
Too long wait time	0.04* (0.01 0.13)	21.6	0.87 (0.37 2.09)	55.1
Satisfaction with treatment by pharmacy staff				
Dissatisfied or somewhat satisfied	Ref	21.6		
Very satisfied	16.79* (6.00 46.98)	80.6		
Satisfaction with the pharmacy experience				
Dissatisfied or somewhat satisfied			Ref	47.4
Very satisfied			2.96* (1.38 6.32)	73.9

aOR, adjusted odds ratio; Ref, referent group.
Mixed effects logistic regression analyses controlled for age, race and ethnicity, education, relationship status, parity, gestational age at initial visit, and prior abortion experience and accounted for clustering by clinical site.
* $P<.05$.

excessively long wait times had lower odds of satisfaction with pharmacy dispensing (adjusted odds ratio [aOR] 0.04, 95% CI 0.01–0.13), and those who reported being very satisfied with the treatment by pharmacy staff had higher odds of satisfaction with pharmacy dispensing (aOR 16.79, 95% CI 6.00–46.98). Those who reported that they were very satisfied with the pharmacy experience had higher odds of being very satisfied with their medication abortion overall compared with those who were somewhat satisfied or dissatisfied with the pharmacy experience (aOR 2.96, 95% CI 1.38–6.32).

DISCUSSION

In this study, medication abortion provision with pharmacist dispensing of mifepristone was effective and acceptable to patients. Among participants with follow-up data, 93% had a complete abortion, and none had an ongoing pregnancy. These outcome proportions are similar to those reported in the literature when the medications are dispensed by a clinician.[18,19] Few patients (1.5%) had adverse events, and none were related to pharmacist dispensing.

We also found that the vast majority of patients were satisfied with the model of care, and overall satisfaction was similar to other studies of medication abortion with clinician-dispensed mifepristone, which have found that 87–88% were satisfied with the method.[19,20] Satisfaction with the pharmacy and treatment by pharmacy staff, reported on the day 2 survey, were somewhat higher than overall satisfaction with medication abortion reported later. This is not surprising given that overall method satisfaction is correlated with symptoms and outcomes of the medication abortion,[21] which might not yet have been apparent by the day 2 survey. The vast majority reported they received adequate information–either from the clinician or pharmacist–and more than 90% indicated their support for pharmacist dispensing of mifepristone in the future.

Although satisfaction with this model was high, the open-ended responses point to areas for improvement that could be addressed through additional training of pharmacists and pharmacy staff. The finding that elements of the pharmacy experience, such as wait time and treatment by the pharmacy staff, were associated with satisfaction with the pharmacy experience, which in turn was associated with overall abortion satisfaction, is similar to research on other pharmacy services.[22]

It is a reassuring finding that one-third of participants who had had a prior medication abortion reported that the current experience of getting the medications at the pharmacy was better. The open-ended responses suggest that patients appreciated the convenience of being able to schedule when to take the medications. Since the FDA approved updated labeling for mifepristone in 2016, patients are no

longer required to take the pill in the facility after it is dispensed,[10] although some state laws still require this. It is also notable that two participants did not proceed with the medication abortion after completing their clinic visit and filling the prescription. Other studies that allow patients to take the mifepristone at home after receiving it in the clinic or that mail the medications patients have also reported that a very small number of patients choose not to proceed with the abortion.[23,24]

One concern that has been raised with allowing clinicians to issue prescriptions for mifepristone is that some pharmacists may refuse to fill the prescription, limiting the feasibility of this model.[25] In our study, the participating pharmacies 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. As a result, all participants were able to fill their prescriptions when they went to the pharmacy. We also collected survey and interview data with the pharmacists at the study pharmacies to evaluate their perceptions of the model, which will be reported separately. Although we did not have challenges with individual pharmacists refusing to dispense mifepristone, we did have difficulty obtaining study approval at chain pharmacies. If the dispensing requirement for mifepristone is eliminated, some pharmacies may refuse to stock the medication, as has been reported for ulipristal acetate emergency contraception,[26] highlighting a potential role for mail-order pharmacies once the Risk Evaluation and Mitigation Strategy is removed.

This study has several strengths, including low loss to follow-up and standardized pharmacist training. It also has several limitations. We had to stop recruitment early because of the COVID-19 pandemic, reaching 89% of our planned minimum sample size. However, the effect of the reduced sample size on the precision of our estimates was small. The sample size is similar to the only other published report on providing medication abortion in the United States without in-clinic dispensing (n=190 with abortion outcome data).[24] In addition, our findings may have limited generalizability given that no chain pharmacy participated; patient experiences at chain pharmacies theoretically may be different. Finally, satisfaction with the pharmacy experience may increase over an extended time as pharmacy staff become more accustomed to dispensing mifepristone.

This study, together with another report of a direct-to-patient telemedicine service in which patients received the medications by mail,[24] demonstrate that medication abortion may be offered with a high level of effectiveness and satisfaction and low prevalence of adverse events without requiring mifepristone to be dispensed in the clinic or medical office. These data further support eliminating the dispensing requirement for mifepristone and allowing pharmacies to dispense the medication.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *No data beyond what is presented in the manuscript will be shared.*

What other documents will be available? *Study protocol and data collection forms will be available.*

When will data be available (start and end dates)? *Study documents will be available from the date of publication for a period of 5 years.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Individuals interested in obtaining study documents should email the corresponding author.*

PEER REVIEW HISTORY

Received October 9, 2020. Received in revised form December 15, 2020. Accepted December 22, 2020. Peer reviews and author correspondence are available at http://links.lww.com/AOG/C228.

Exhibit 8

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 28, 2000

FROM: [redacted] /S/ SEP 28 2000

SUBJECT: [redacted] Memo

TO: NDA 20-687 MIFEPREX (mifepristone) Population Council

This memo documents the approval action concerning the Population Council's NDA for mifepristone for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The application was initially submitted to the Food and Drug Administration (FDA) on March 14, 1996. The Reproductive Health Drugs Advisory Committee met on July 19, 1996 and voted that benefits exceeded risk for this drug product with 6-yes, 0-no, and 2 abstentions. An approvable action letter was issued September 18, 1996 citing deficiencies in areas of Clinical (distribution system), Chemistry/Manufacturing and Controls, Biopharmaceutics, and Labeling. A complete response was received August 18, 1999. The last action by the Office was on February 18, 2000. That approvable action letter listed application deficiencies consisting of Chemistry/Manufacturing and Controls, Labeling, and the Distribution System issues. The Population Council submitted a complete response on March 30, 2000. After a brief summary of effectiveness and safety, this memo addresses those outstanding issues listed in the last action letter, Phase 4 commitments, and other issues.

Summary of Effectiveness and Safety

Effectiveness and safety data were derived from one U.S. clinical trial and two French trials. Effectiveness was defined as the complete expulsion of products of conception without the need for surgical intervention.

The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period. Demographic data showed racial composition of the U.S. trial was similar to the overall U.S. general population. Medical abortion was complete in 92.1% of 827 subjects. Surgical intervention was performed in 7.9% of subjects: 1.6% had medically indicated interventions (1.2% for heavy bleeding), 4.7% had incomplete abortions, 1.0% had ongoing pregnancies, and 0.6% had intervention at the patient's request. One of the 859 patients received a blood transfusion.

The two French trials enrolled a total of 1,681 women providing effectiveness outcomes and 1,800 women providing safety information. Medical abortion was complete in 95.5% of the 1681 subjects. Surgical intervention was performed in 4.5% of subjects: 0.3% for bleeding, 2.9% for incomplete abortions, and 1.3% for ongoing pregnancies. Of the 1,800 women, 2 patients received blood transfusions.

The Advisory Committee reviewed the French data in 1996 and voted 6-yes and 2-no for data supporting efficacy, 7-yes and 1-abstention for data supporting safety. As stated above, the overall vote for benefits exceeding risk was 6-yes, 0-no, and 2-abstentions. During the second review cycle in 1999, the committee received a copy of the U.S. study report, as they requested, to provide FDA with comments. None were received. The U.S. trial data confirms the effectiveness and safety of the product.

APPEARS THIS WAY
ON ORIGINAL

Exhibit 8

Chemistry/Manufacturing

In May, 2000 the Population Council informed the Division of Reproductive and Urologic Drug Products that the bulk drug substance maker had changed manufacturing processes last summer. New analytic, physical, and stability data were received and reviewed and found to be adequate to ensure the quality of the drug manufacturing was preserved.

An inspection of the bulk drug substance maker was performed on July 24-28, 2000. Deficiencies were cited and the manufacturer corrected these. These corrections were found acceptable.

Because the drug is being distributed directly to qualified physicians, there is minimal chance for drug name confusion and I agree with the name, Mifeprex.

Labeling

Labeling is important to educate prescribers and patients about the safe and effective use of the drug and to inform health professionals about adverse event risks. The 1996 Advisory Committee strongly supported education of users of mifepristone. By coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic pregancies (and other requirements), goals of safe and appropriate use may be achieved. The drug's labeling is now part of a total risk management program that will be summarized below. The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement will together constitute the approved product labeling to ensure any future generic drug manufacturers will have the same risk management program.

The labeling for mifepristone has been revised to provide information about how to report adverse events. FDA and the Population Council agree that a black box will highlight special items related to the drug. In addition, FDA has determined that a Medication Guide for this drug will help ensure dispensers provide important information to patients to enhance compliance with the regimen for safety and efficacy. Furthermore, a patient agreement fosters active patient education and participation in this regimen. The Population Council will provide these educational materials (the professional labeling, the Medication Guide, the patient agreement form, and the Prescriber's Agreement form). The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement must be read, understood, and attested to by physicians who meet prescribing qualifications (discussed below).

Black Box

21 CFR 201.57(e) permits FDA to require a black box warning for special problems, particularly those that may lead to death or serious injury. The Population Council agreed in its July 5, 2000 submission to a black box warning. It was agreed that the box would contain the following:

> "If Mifeprex results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions of whom to call and what to do in the event of an emergency following administration of Mifeprex.
>
> Prescribers should make sure the patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement."

Misoprostol Administration

The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. The data were anecdotal off-label experience with

a vaginal misoprostol regimen, an observational study about home use in Guadeloupe, and a U.S. clinical study of home use of a different regimen with different drug doses. The only study that commented on whether home use led to correct use was the Guadeloupe study reporting that 4% of patients who took misoprostol at home did it incorrectly. Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.

Early in drug development, a mandatory observation period of 3-4 hours was instituted in clinical trials worldwide when a prostaglandin analogue, sulprostone, was used with mifepristone and felt to have some cardiovascular risk. This drug is no longer being used with mifepristone and is not a marketed drug in the U.S.; therefore, the rationale for an observation period is moot. There is no more likelihood of an adverse event occurring in the few hours after misoprostol administration than during the entire study period.

Therefore, as a consequence of this re-evaluation, the labeling currently reads that the patient returns on Day 3 for misoprostol and is given instructions about adverse events and whom to contact for questions and emergencies.

Access to Health Care and Emergency Services

FDA agreed with the Population Council that access to health care and emergency services is critical for the safe and effective use of the drug. The clinical trials ensured access to services. The labeling has a black box highlighting the possible need for surgical intervention and either the provision of access to these services by the prescriber or through referral. The labeling has a contraindication if there is no access to medical facilities for emergency services. The Patient Agreement emphasizes the need to know what to do in the case of an emergency.

Patient Agreement Form

Patients should be informed about the indication of the drug and how it is given. They must understand the type of regimen they are about to commit to and its risks and benefits. The signed agreement form will be given to the patient for her reference and another kept in the medical record. The Population Council has committed to auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms.

Biopharmaceutics

This review cycle, the clinical biopharmaceutical reviewers evaluated new data in the published literature regarding the metabolism of mifepristone by the P450 3A4 system. Mifepristone is a substrate and this may inhibit drug metabolism of certain drugs and induce metabolism of others. This information was placed in the professional labeling and patients are instructed in the Medication Guide that use of other drugs may interfere with actions of mifepristone and misoprostol.

Pharmacology-Toxicology

Current literature on the effects of human fetal exposure to mifepristone and misoprostol or mifepristone alone was reviewed to ensure risk information was current. Many of the case reports of malformation concern the unsuccessful use of misoprostol for abortion, resulting in limb, facial, cranial, and other abnormalities. Many reports were retrospective in nature, subject to reporting and recall bias. Nevertheless, the risk of malformation is very important to address. This drug's indication is for pregnancy termination. The labeling, Medication Guide, process of obtaining patient agreement on medical abortion, and the commitment of the physicians through their signed Prescriber's Agreement are all meant to ensure women are completely informed about the process and make a commitment to follow through.

The labeling for Mifeprex states that it is used with misoprostol for termination of pregnancy of 49 days or less. Human data on mifepristone and misoprostol used in this timeframe is available. Safety Update Report #3 submitted on March 31, 2000 contains Exelgyn Laboratories Periodic Safety Update Report #9 for the period of September 1, 1998 to November 30, 1999. It lists 38 on-going pregnancies with mifepristone plus misoprostol. The Lancet published a letter in July 1998 from Exelgyn in which they mention that they had reviewed 71 cases of continuing pregnancies after failed early termination of pregnancy occurring from 1987 to 1998 and found no reported cases of malformation associated with use of mifepristone and misoprostol. There was one report of sirenomelia and cleft palate in a patient who had a therapeutic termination at week 7 gestation associated with mifepristone use alone. On July 6, 1999 the European Summary of Product Characteristics contains a statement for mifepristone that in humans, the reported cases do not allow a causality assessment for mifepristone alone or used with a prostaglandin. On August 21, 2000 the sponsor provided Exelgyn's 12/1/99 to 5/31/00 Periodic Safety Update on pregnancy outcomes following early pregnancy exposure. The current labeling has these new data on 82 pregnancies exposed to mifepristone only (40) and mifepristone used with misoprostol (42). FDA agrees that no conclusion can be made from the data at this time. Information on the possibility of a risk of malformation, including the above information as well as the anecdotal reports, is nevertheless included in the professional labeling, Medication Guide, and Patient Agreement. The Population Council has committed to continuing ongoing surveillance of human malformation risk.

Medication Guide

This product will be approved with a Medication Guide which dispensers must provide with the drug. It is important for patients to be fully informed about the drug, as well as the need for follow up, especially on Day 14 to confirm expulsion. A Medication Guide was determined to be necessary to patients' safe and effective use of the drug. The drug product is important to the health of women and the Medication Guide will encourage patient adherence to directions for use. Patient adherence to directions for use and visits is critical to the drug's effectiveness and safety.

Distribution System

Since 1996, FDA and the Population Council have agreed, as publicly discussed with the Reproductive Drug Products Advisory Committee, that once approved, the drug will be distributed directly to physicians. It will not be available from pharmacies. There were also discussions about the qualifications of the physicians receiving mifepristone for dispensing. The Committee also stated it was important that women have access to medical abortion as this new therapeutic option may offer women avoidance of a surgical procedure.

In January 2000, the Population Council provided its initial plan for drug distribution. This plan was resubmitted in its complete response of March 30, 2000. This plan had acceptably addressed the issue of physical security of the drug. The distribution system plan stated specific requirements imposed on and by distributors of the drug, including procedures for storage, dosage tracking, damaged product returns, and other matters. See Subpart H of this memo for more details. Other aspects of the distribution system are addressed below.

Physician Qualifications

Physician qualifications were discussed within CDER, the Agency, and with the Population Council. FDA also discussed physician qualifications with a special government employee with expertise in early pregnancy. The Population Council proposed that the drug be directly distributed to qualified physicians, as opposed to other types of health care professionals (midwives, physician's assistants, nurse practitioners, etc.). This restriction was supported by the discussions of the 1996 Advisory Committee. In fact, the clinical trial data was derived from the experience of physicians using this drug. Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician, from

dispensing the drug to patients, provided state laws permit this. Should data be provided to amend the restriction to physicians, FDA will consider them.

The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and/or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists. All patients were within one hour of emergency facilities or the facilities of the principle investigator.

The role of ultrasound was carefully considered. In the clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, dating pregnancies occurs through using other clinical methods, as well as through using ultrasound. Ultrasound information can be provided to the prescribing physicians to guide treatment, but this information can be obtained through consultation referral from an ultrasound provider and does not necessarily need to be obtained by the prescriber him/herself. The labeling recommends ultrasound evaluation as needed, leaving it to the medical judgement of the physician.

The Population Council proposed that any physician who could date pregnancies and diagnose ectopic pregnancies should be able to receive the drug from the distributor. These two qualifications alone limit the number of physicians who will be eligible to receive mifepristone from the Population Council's distributor(s) to those physicians who are very familiar with managing early pregnancies. These two qualifications also are performance-based standards and do not limit providers of mifepristone to specific medical subspecialties. Education about the use of the drug is described above in the Labeling section of this memo. Because qualified physicians will be using this drug, there is no need for special certification programs. The current labeling and distribution system states physician need not have skills for handling surgical interventions, but could provide referral to services for incomplete abortion and emergency care. The Population Council stated that current medical practice is structured on referral of patients who need surgery (for example, women with a spontaneous incomplete abortion or a cardiologist's patient who needs by-pass grafts) to a physician possessing the skills to address the problem. Moreover, within the U.S. clinical trial, 11 patients out of roughly 850 patients needed surgical intervention to handle bleeding, the most important urgent adverse event associated with this drug, and 3 of these patients were handled by non-principal investigators such as the emergency room and non-study gynecologist. This suggests that patients will get the needed surgical intervention by either their physician or another physician with the needed skills. Referral to a hospital for emergency services does not mean having admitting privileges, but having the ability and the responsibility to direct patients to hospitals, if needed. The professional labeling and the Medication Guide highlight that surgery may be needed and patients need to know if the provider of mifepristone will furnish surgical intervention or if the patient will be referred. If the latter, the treating health care provider must give the patient the name, address, and phone number of this referred provider. To ensure that the quality of care is not different for patients who are treated by physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study. This monitoring study incorporates study questions of four of the original six Phase 4 commitments. See Phase 4 Commitments for additional information.

Finally, the one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services. This concern has been dealt with through the labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated.

APPEARS THIS WAY
ON ORIGINAL

Subpart H

In the February 18, 2000 approvable letter, FDA stated that the eventual approval of this drug would be under Subpart H (21 CFR 314.500-314.560). This subpart applies to certain new drugs that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. FDA has determined that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H. The meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure. Subpart H applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with special skills or experience. In the case of mifepristone, the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications. Under 21 CFR 314.520, distribution of mifepristone is restricted as described below.

- Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately
  - Ability to diagnose ectopic pregnancies
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
  - Has read and understood the prescribing information of Mifeprex
  - Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
  - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
  - Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
  - Must record the Mifeprex package serial number in each patient's record

- With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:
  - Secure manufacturing, receiving, and holding areas for the drug
  - Secure shipping procedures, including tamper-proof seals
  - Controlled returns procedures
  - Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
  - Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
  - Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

The Population Council agreed to approval under Subpart H in their letter of September 15, 2000.

APPEARS THIS WAY
ON ORIGINAL

Phase 4 Commitments

In 1996, the Population Council committed to 6 post-marketing studies: 1) to monitor the adequacy of the distribution and credentialing system; 2) to follow up on the outcome of a representative sample of mifepristone treated women who have surgical abortion because of method failure; 3) to assess the long term effects of multiple use of the regimen; 4) to ascertain frequency with which women follow the complete treatment regimen and the outcome of those who do not; 5) to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke; 6) to ascertain the effect of the regimen on children born after treatment failure.

During this review cycle, items 1, 2, 4 and 5 were revised and integrated into a monitoring study to ensure providers who did not have surgical intervention skills and referred patients for surgery had similar patient outcomes as those patients under the care of physicians who possessed surgical skills (such as those in the clinical trial). This study specifically addresses adequacy of qualifications (#1). FDA reviewed the protocols from the Population Council submitted on September 7, 2000 and provided a revised protocol on September 13, 2000 in which the investigators collect data on safety outcomes (#2), return for their follow up visits (#4), and include all ages (#5) and collect smoking status (#5). Commitment #2 was defined by the Advisory Committee discussions of 1996 surrounding the question of whether certain physician specialties would have higher rates of problems encountered with medical abortion. This study specifically will investigate the performance of specialties with surgical skills compared to those that refer for surgical interventions with respect to incidence of medical abortion failures.

The Population Council agrees to study ongoing pregnancies and their outcomes through a surveillance, reporting, and tracking system (#6). This protocol summary and a summary for the monitoring system was received on September 19, 2000 and both were found to be adequate.

The Population Council asked that Commitment #3 (to assess the long term effects of multiple use of the regimen) be waived because it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug, especially given privacy issues. In addition, the pharmacology of mifepristone does not suggest any carry over effect after one-time administration. The Agency agrees with this assessment.

As a note, this cycle the Population Council provided new data concerning Commitment #5 (to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke), from Spitz et al. This study had 106 women ages 35 years or older as well as 51 subjects under age 20, all of whom were 49 days or less since their last menstrual period. The data on the older women is informative and of meaningful sample size. FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Sptiz data actually suggests a trend towards increased success of medical abortion with younger patients. However, as these age groups were not part of the NDA indication and the data on safety and effectiveness were only reviewed for the indication's age group (18-35 years of age), the trials excluded patients younger than 18 years old, and the raw data from Sptiz have not been submitted for review, the labeling states the safety and efficacy in these groups have not been studied. The Population Council will collect outcomes in their Phase 4 studies of women of all ages to further study this issue. With respect to smokers, the Population Council will study smokers of various ages to collect safety information. In sum, the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996.

The postmarketing audit of signed Patient Agreement forms was discussed above.

Public Comments Considered

The Food and Drug Administration received over 1,000 letters or emails from the public about mifepristone. Most comments objected to various restrictions of the drug's distribution. For example, many letters opposed press reports of an alleged FDA public registry of doctors who dispense mifepristone. Other letters focused on the research uses of mifepristone for neurologic and oncologic diseases and the concern that restricting distribution after approval would constrain off-label uses. Still other letters expressed misunderstanding that experimental indications that are subject to INDs would be limited by an approval of mifepristone with distribution restrictions. These comments were reviewed and considered.

Risk Management Program

Risk management for a drug has the goal of optimizing the use of a product by maximizing its benefits and minimizing its risks. Interventions to manage risk include education to physicians, patients, and the public, labeling (including warnings, precautions, contraindications, dosage and administration, and Medication Guide), restriction of product use or supply, and packaging changes. This drug is being approved under Subpart H (restrictions on distribution) as part of the risk management program. The Population Council and FDA have identified the areas below, among others, that contribute to drug safety and effectiveness:

1. Proper selection of patients via physicians who are qualified to do so by dating pregnancies and diagnosing ectopics,
2. Qualified physicians to administer or supervise the administration of the medication
3. Compliance with the regimen by physicians and patients through education and monitoring
4. Safety and effectiveness information that fully informs patients and physicians about the risks and benefits of the treatment
5. Evaluation of physician qualifications through Phase 4 studies has been discussed in above sections.
6. Physical packaging in unit of dosing to ensure proper dose and provision of Medication Guide with each dose
7. Active patient participation in the treatment through the Patient Agreement and Medication Guide with an audit of signed Patient Agreement to ensure compliance
8. Active programs to get physicians to report adverse events and ongoing pregnancies to provide accurate risk information
9. Commitment to review and revise the risk management program for improved public health

All components of this risk management program have been discussed above, including the Medication Guide, the labeling that includes the Prescriber's and Patient Agreement forms, approval under Subpart H, and Phase 4 studies to evaluate risk management interventions and to gather data on risks.

In summary, all approval issues related to the NDA have been addressed adequately.

APPEARS THIS WAY
ON ORIGINAL

Exhibit 9

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–N–0174]

Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing this notice to notify holders of certain prescription new drug and biological license applications that they will be deemed to have in effect an approved risk evaluation and mitigation strategy (REMS) under the Food and Drug Administration Amendments Act of 2007 (FDAAA). Holders of applications deemed to have in effect an approved REMS are required to submit a proposed REMS to FDA.

DATES: Submit proposed REMSs to FDA by September 21, 2008.

ADDRESSES: Written communications regarding the applicability of this notice to a specific product should be identified with Docket Number FDA–2008–N–0174 and submitted to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic communications to *http://www.regulations.gov*. Information about FDA implementation of FDAAA is available on the Internet at *http://www.fda.gov/oc/initiatives/advance/fdaaa.html*.

FOR FURTHER INFORMATION CONTACT: Mary Dempsey, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 4326, Silver Spring, MD 20993–0002, 301–796–0147.

SUPPLEMENTARY INFORMATION:

I. Introduction

On September 27, 2007, the President signed into law FDAAA (Public Law 110–85). Title IX, subtitle A, section 901 of FDAAA created new section 505–1 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355–1). Section 505–1(a) of the act authorizes FDA to require persons submitting certain applications[1] to submit and implement a REMS if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug and informs the holder of the application for the drug of the determination. Section 909 of FDAAA provides that Title IX, subtitle A takes effect 180 days after its enactment, which is March 25, 2008.

FDAAA also contains REMS requirements for drug and biological products approved before the effective date of Title IX, subtitle A. Section 909(b)(1) of FDAAA specifies that a ''drug that was approved before the effective date of this Act is * * * deemed to have in effect an approved risk evaluation and mitigation strategy under section 505–1 of the Federal Food, Drug, and Cosmetic Act * * * if there are in effect on the effective date of this Act elements to assure safe use—(A) required under section 314.520 or section 601.42 of title 21, Code of Federal Regulations; or (B) otherwise agreed to by the applicant and the Secretary [of Health and Human Services] for such drug.''

Section 909(b)(3) of FDAAA states: ''Not later than 180 days after the effective date of this Act, the holder of an approved application for which a risk evaluation and mitigation strategy is deemed to be in effect * * * shall submit to the Secretary a proposed risk evaluation and mitigation strategy. Such proposed strategy is subject to section 505–1 of the Act as if included in such application at the time of submission of the application to the Secretary.''[2]

Section 909(b)(2) of FDAAA states that a REMS for a drug deemed to have a REMS consists of the timetable required under section 505–1(d) of the act and any additional elements under section 505–1(e) and (f) of the act in effect for the drug on the effective date of FDAAA.

The purpose of this notice is to identify those drugs that FDA has determined will be deemed to have in effect an approved REMS and to notify holders of applications for such drugs that they are required to submit a proposed REMS by September 21, 2008. FDA is developing guidance on the preferred content and format of a proposed REMS required to be submitted under section 909(b) of FDAAA and will issue it as soon as possible.

II. List of Drug and Biological Products Deemed to Have a REMS

Drug and biological products deemed to have in effect an approved REMS are those that on March 25, 2008 (the effective date of Title IX, subtitle A of FDAAA), had in effect ''elements to assure safe use.'' ''Elements to assure safe use'' include the following: (1) Health care providers who prescribe the drug have particular training or experience, or are specially certified; (2) pharmacies, practitioners, or health care settings that dispense the drug are specially certified; (3) the drug is dispensed to patients only in certain health care settings, such as hospitals; (4) the drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results; (5) each patient using the drug is subject to certain monitoring; or (6) each patient using the drug is enrolled in a registry (see section 505–1(f)(3) of the act).

Some applications approved before the effective date of FDAAA Title IX, subtitle A contain these elements to assure safe use.[3] Some of these applications were approved under § 314.520 (21 CFR 314.520) or § 601.42 (21 CFR 601.42). Others were not approved under part 314, subpart H or part 601, subpart E, but still contain elements to assure safe use that were agreed to by the applicant and the Secretary for such drug. Since 2005, these elements typically appeared in approved risk minimization action plans (RiskMAPs) (see the guidance for industry entitled ''Development and Use of Risk Minimization Action Plans'' (70 FR 15866, March 29, 2005)).

FDA has reviewed its records to identify applications that were approved before the effective date of Title IX of FDAAA with elements to assure safe use and has identified the drug and biological products listed in table 1 of this document as those that will be deemed to have in effect an approved REMS.

[1] Section 505(p)(1) of the act (21 U.S.C. 355(p)(1)) states that section 505–1 of the act applies to applications for prescription drugs approved under section 505(b) or (j) of the act and applications approved under section 351 of the Public Health Service Act (42 U.S.C. 262).

[2] Title IX, subtitle A of FDAAA, which includes section 909, takes effect March 25, 2008; 180 days after that date is September 21, 2008.

[3] These plans sometimes contain other elements to minimize risk such as a Medication Guide (21 CFR part 208) or a communication/educational plan for health care providers or patients. A drug will not be deemed to have a REMS if it has only a Medication Guide, patient package insert, and/or communication plan (see section 505–1(e)(2) and (e)(3) of the act).

Exhibit 9

2019 CP 000669

TABLE 1.—PRODUCTS DEEMED TO HAVE IN EFFECT AN APPROVED REMS

Generic or Proper Name	Brand Name	Application Number[1]	Date of Approval[2]
Abarelix	Plenaxis[3]	NDA 21–320	11/25/2003
Alosetron	Lotronex	NDA 21–107	02/09/2000
Ambrisentan	Letairis	NDA 22–081	06/15/2007
Bosentan	Tracleer	NDA 21–290	11/20/2001
Clozapine	Clozaril	NDA 19–758 ANDA 74–949 ANDA 75–417 ANDA 75–713 ANDA 75–162 ANDA 76–809	09/26/1989 11/26/97 5/27/99 11/15/02 4/26/05 12/16/05
	Fazaclo ODT	NDA 21–590	02/09/2004
Dofetilide	Tikosyn	NDA 20–931	10/01/1999
Eculizumab	Soliris	BLA 125166	03/16/2007
Fentanyl PCA	Ionsys[3]	NDA 21–338	05/22/2006
Fentanyl citrate	Actiq	NDA 20–747	11/04/1998
Isotretinoin	Accutane Amnesteem Claravis	NDA 18–662 ANDA 75–945 ANDA 76–135 ANDA 76–356	05/07/1982 11/2002 04/2003 04/2003
	Sotret	ANDA 76–041 ANDA 76–503	12/2002 06/2003
Lenalidomide	Revlimid	NDA 21–880	12/27/2005
Mifepristone	Mifeprex	NDA 20–687	09/28/2000
Natalizumab	Tysabri	BLA 125104	11/23/2004
Small pox (Vaccinia) Vaccine, Live	ACAM2000	BLA 125158	08/31/2007
Sodium oxybate	Xyrem	NDA 21–196	07/17/2002
Thalidomide	Thalomid	NDA 20–785 NDA 21–430	07/16/1998

[1] New drug application (NDA), abbreviated new drug application (ANDA), biologics license application (BLA).
[2] The original date of approval of the drug. FDA may have required elements to assure safe use at a later date.
[3] Product is not currently marketed in the United States.

FDA is further asking members of the public to please notify the agency if they are aware of applications that have not been identified in this document and that they believe should be deemed to have in effect an approved REMS. Please provide the information to Mary Dempsey, Risk Management Coordinator (see the **FOR FURTHER INFORMATION CONTACT** section of this document).

Any application holder that believes its product identified in this notice should not be on the list of drug or biological products that will be deemed to have in effect an approved REMS should submit a letter identified with Docket Number FDA–2008–N–0174 to the Division of Dockets Management (see **ADDRESSES**) stating why the application holder believes its product was improperly identified in this notice. FDA will notify the application holder within 30 days of receipt of the letter of its determination.

Dated: March 19, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8–6201 Filed 3–26–08; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committees: Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

Exhibit 10

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-022

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated November 4, 2015, received November 5, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

This Prior Approval supplemental new drug application proposes modifications to the approved risk evaluation and mitigation strategy (REMS) for Mifeprex to establish a single, shared system (SSS) REMS for mifepristone products for the medical termination of intrauterine pregnancy and updates to the approved Prescribing Information, Medication Guide, and REMS materials including the Prescriber Agreement and Patient Agreement Forms to incorporate language reflecting the proposed SSS REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at:

Exhibit 10

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The most recent modification was approved on March 29, 2016. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS establish a SSS REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Mifeprex and ANDAs referencing Mifeprex, called the Mifepristone REMS Program.

Your proposed modified REMS, submitted on January 25, 2018, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the initial approval of the SSS REMS (04/11/19) and every three years thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Both cumulative data from the date of the initial approval of the SSS REMS (04/11/19) and data from the reporting period (i.e., from the preceding Mifeprex REMS assessment cut-off date to the cut-off date for the Mifepristone REMS Program.)

REMS Assessment Plan

Provide each metric for the current reporting period and cumulative for the RLD and ANDA(s):

1. Number of prescribers enrolled
2. Number of prescribers ordering mifepristone
3. Number of healthcare providers who attempted to order mifepristone who were not enrolled; describe actions taken
4. Number of women exposed to mifepristone
5. Summary and analysis of any program deviations and corrective action taken
6. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) If the new indication for use introduces unexpected risks: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use: Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous

REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687/S-000/ SECONDARY TRACKING NUMBER
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

Or

NEW SUPPLEMENT FOR NDA 020687/S-000/ SECONDARY TRACKING NUMBER
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

Or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page

of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information
  - Medication Guide
- REMS

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/

(b) (6)

04/11/2019 02:13:59 PM

Exhibit 11

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020687Orig1s020

Trade Name:	Mifeprex Tablets
Generic Name:	mifepristone
Sponsor:	Danco Laboratories, LLC
Approval Date:	March 29, 2016
Indication:	For use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS

Exhibit 11

CENTER FOR DRUG EVALUATION AND RESEARCH

020687Orig1s020

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	X
Summary Review	X
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	X
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology / Virology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-020

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated July 17, 2015.

This "Prior Approval" supplemental new drug application proposes to provide for use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because the use of this product before menarche is not indicated, and we have determined that you have fulfilled the pediatric study requirement for post-menarcheal patients.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The REMS consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS included revisions to both the prescriber and patient agreement forms.

Other changes proposed in the efficacy supplement prompted additional revisions to the Mifeprex REMS materials. During review of this efficacy supplement, we also assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks.

After consultations between the (b) (6) and the (b) (6) we have determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS. The REMS modifications submitted by you on March 29, 2016 are approved.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Mifeprex outweigh its risks. The

Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on July 17, 2015, and appended to this letter, is approved as amended. The modified REMS consists of elements to assure safe use (A, C and D), an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on June 8, 2011.

The REMS assessment plan will include the information submitted to FDA on March 29, 2016.

The revised REMS assessment plan must include, but is not limited to, the following:

REMS Assessment Plan

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative).
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6) .

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

Exhibit 12

Center for Drug Evaluation and Research (CDER)

[redacted]

Application Type	NDA and ANDA
Application Number	020687 and 91178
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	December 16, 2021

Exhibit 12

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

Table of Contents

EXECUTIVE SUMMARY 4

1. Introduction 5
2. Background 5
   - 2.1. PRODUCT AND REMS INFORMATION 5
   - 2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW 7
3. Rationale for Proposed REMS Modification 9
   - 3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS 10
   - 3.2. EVALUATION OF THE EVIDENCE 10
   - 3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A) 12
   - 3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D) 14
   - 3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C) 19
4. Discussion 36
5. Conclusions and Recommendations 41
6. References 42
7. Appendix 45

EXECUTIVE SUMMARY

This review provides the (b) (6) ((b) (6) and (b) (6) ((b) (6) 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. (b) (4) 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 (b) (4) shipments representing (b) (4) 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 (b) (6) ((b) (6) 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 (b) (6). Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized April 12, 2021.

p (b) (6) Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 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).

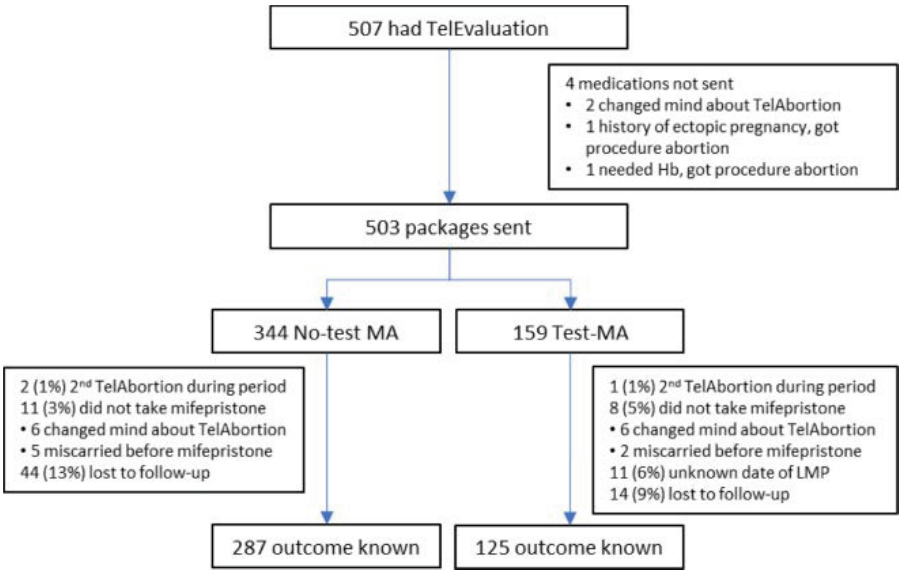
Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider 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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Number 225: Medication abortion up to 70 days of gestation. Obstet Gynecol 2020;136(4): e31-e47 and in Contraception 2020; 102:225-236.

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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)
References included in the REMS review
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Grossman D et al. Obstet Gynecol 2021; 137 (4): 613-622.	
Winikoff B et al. Obstet Gynecol 2012; 120: 1070-1076 reviewed in 2016 clinical memo	
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/

(b) (6)
12/16/2021 10:22:50 AM

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12/16/2021 10:49:46 AM

(b) (6)
12/16/2021 10:59:01 AM

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12/16/2021 11:08:07 AM

Exhibit 13

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Quentin L. Van Meter, M.D., FCP
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December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

(1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:

- Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.

- Dosage and Administration:
  - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

  - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
w ww.fda.gov

Exhibit 13

- 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

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[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.

[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:

[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.

[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.

Exhibit 14

U.S. FOOD & DRUG ADMINISTRATION

NDA 020687

REMS MODIFICATION NOTIFICATION

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for mifepristone was originally approved on June 8, 2011, and your single shared system REMS (SSS REMS) was approved on April 11, 2019. Your last SSS REMS modification was approved May 14, 2021. The SSS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that your approved REMS for mifepristone must be modified 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.

This determination is based on a review of published literature, safety information collected during the COVID 19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

Elements to Assure Safe Use: We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in person dispensing requirement") is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in person dispensing will also minimize the burden on the healthcare delivery system of complying with the REMS.

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of serious

Exhibit 14

complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, 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 must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS must include a timetable for submission of assessments.
The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS, and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your NDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687/S-000
PROPOSED REMS MODIFICATION-AMENDMENT

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

If you have any questions, call [redacted] (b) (6), at [redacted] (b) (6).

Sincerely,

{See appended electronic signature page}

[redacted] (b) (6)

Center for Drug Evaluation and Research

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/

(b) (6)

12/16/2021 03:09:07 PM

Exhibit 15

U.S. FOOD & DRUG ADMINISTRATION

ANDA 091178

REMS MODIFICATION NOTIFICATION

GenBioPro, Inc.
c/o (b)(4)/TS-CI; (b)(6)/PPI

Attention: (b)(4)/TS-CI; (b)(6)/PPI

Dear (b)(4)/TS-CI; (b)(6)/PPI:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for mifepristone tablets.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Shared System (SS) REMS for mifepristone consists of elements to assure safe use, and an implementation system.

In accordance with section 505-1(g)(4)(B) of the FD&C Act, we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

Elements to Assure Safe Use: We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will reduce the burden on the healthcare delivery system of complying with the REMS.

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

Exhibit 15

serious complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers who prescribe the drugs 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 must include an implementation system to monitor, evaluate, and work to improve the implementation of the ETASU (as outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your ANDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B) of the FD&C Act, you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A) of the FD&C Act.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

ANDA 091178/S-000
PROPOSED REMS MODIFICATION-AMENDMENT

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

If you have any questions, call (b)(6)/PPI .

Sincerely,

{See appended electronic signature page}

(b)(6)/PPI

Center for Drug Evaluation and Research

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

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/

(b)(6)/PPI

12/16/2021 03:21:22 PM

Exhibit 16

[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

Exhibit 16

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3
1. Introduction 4
2. Background 4
2.1. Product Information and REMS Information 4
2.2. Regulatory History 6
3. Review of Proposed REMS Modification 8
3.1. REMS Goal 8
3.2. REMS Document 8
3.3. REMS Requirements 9
3.3.1. Addition and Removal of ETASU 9
3.3.2. REMS Participant Requirements and Materials 9
3.3.2.1. Prescriber Requirements 9
3.3.2.2. Patient Requirements 11
3.3.2.3. Pharmacy Requirements 12
3.3.2.4. Distributor Requirements 15
3.3.3. REMS Sponsor Requirements 15
3.3.3.1. Sponsor Requirements to Support Prescriber Certification 15
3.3.3.2. Sponsor Requirements to Support Pharmacy Certification 16
3.3.3.3. Sponsor Implementation Requirements 16
3.4. REMS Assessment Timetable 16
4. Supporting Document 17
5. REMS Assessment Plan 17
6. Discussion 19
7. Conclusions and Recommendations 21
8. References 21
9. Appendices 22

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

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.

DANCO
Support • Progress • Options

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

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.**

The REMS Assessment Plan must include but is not limited to the following items.

Program Implementation and Operations

1. REMS Certification Statistics
   a. Prescribers
      i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
      ii. Number and percentage of newly certified prescribers
      iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

   b. Pharmacies
      i. Number of certified pharmacies
      ii. Number and percentage of newly certified pharmacies
      iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)
   c. Wholesalers/Distributors
      i. Number of authorized wholesalers/distributors
      ii. Number and percentage of newly authorized wholesalers/distributors
      iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data
   a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
   b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data
   a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
      i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
      ii. The number of audits expected, and the number of audits performed
      iii. The number and type of deficiencies noted
      iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
      v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)

vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)

b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:

i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)

ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):

1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
2. The source of the non-compliance data (e.g., self-reported, audit, other)
3. A root cause analysis of the non-compliance
4. Actions to prevent future occurrences and outcomes of such actions

iii. Prescriber compliance

1. Number and percentage of certified prescribers who became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

iv. Pharmacy compliance

1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
3. Number and percentage of pharmacies that became decertified as a result of non-compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

v. Wholesaler/distributor compliance

1. Number of healthcare providers who successfully ordered mifepristone who were not certified
2. Number of non-certified pharmacies that successfully ordered mifepristone
3. Number of shipments sent to non-certified prescriber receiving locations
4. Number of shipments sent to non-certified pharmacy receiving locations

5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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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Exhibit 17

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020687Orig1s025

Trade Name:	Mifeprex Tablets 200 mg
Generic or Proper Name:	Mifepristone
Sponsor:	Danco Laboratories, LLC
Approval Date:	January 3, 2023
Indication:	For modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program.

Exhibit 17

CENTER FOR DRUG EVALUATION AND RESEARCH

020687Orig1s025

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	X
Summary Review	X
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

APPROVAL LETTER

U.S. FOOD & DRUG ADMINISTRATION

NDA 020687/S-025

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your supplemental new drug application (sNDA) dated and received June 22, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets, 200 mg.

This Prior Approval sNDA provides for modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program. This SSS REMS is known as the Mifepristone REMS Program.

APPROVAL & LABELING

We have completed our review of the supplemental application, as amended. It is approved effective the date of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Mifepristone REMS Program, of which Mifeprex is a member, was originally approved on April 11, 2019, and the most recent REMS modification was approved on May 14, 2021. The Mifepristone REMS Program consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Mifeprex outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Notification letter dated December 16, 2021. In addition the following modifications were communicated 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*).

Your proposed modified REMS, received on June 22, 2022, amended and appended to this letter, is approved. The modified REMS consists of the elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The modification of the approved REMS must be fully implemented within 120 calendar days of this letter.

This shared system REMS, known as the Mifepristone REMS Program, currently includes those products listed on the FDA REMS website[3].

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the approval of the modified SSS REMS (1/3/2023) and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Certification Statistics
   a. Prescribers
      i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
      ii. Number and percentage of newly certified prescribers
      iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

   b. Pharmacies

[3] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

i. Number of certified pharmacies
ii. Number and percentage of newly certified pharmacies
iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)

c. Wholesalers/Distributors
i. Number of authorized wholesalers/distributors
ii. Number and percentage of newly authorized wholesalers/distributors
iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data
a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data
a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
ii. The number of audits expected, and the number of audits performed
iii. The number and type of deficiencies noted
iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)
vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)

b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:
i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)
ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):
1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
2. The source of the non-compliance data (e.g., self-reported, audit, other)
3. A root cause analysis of the non-compliance

4. Actions to prevent future occurrences and outcomes of such actions

iii. Prescriber compliance

1. Number and percentage of certified prescribers who became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

iv. Pharmacy compliance

1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
3. Number and percentage of pharmacies that became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

v. Wholesaler/distributor compliance

1. Number of healthcare providers who successfully ordered mifepristone who were not certified
2. Number of non-certified pharmacies that successfully ordered mifepristone
3. Number of shipments sent to non-certified prescriber receiving locations
4. Number of shipments sent to non-certified pharmacy receiving locations
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

Overall Assessment of REMS Effectiveness

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a

proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively,

updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000/
PRIOR APPROVAL SUPPLEMENT

PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov
.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - REMS Document
  - Prescriber Agreement
  - Patient Agreement Form
  - Pharmacy Agreement Form

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/

(b) (6)

01/03/2023 05:35:41 PM

Exhibit 18

(b)(6)/PPI

Response to Consult Request from (b)(6)/PPI **CDER**

To: (b)(6)/PPI (b)(6)/PPI (b)(6)/PPI (b)(6)/PPI

From: (b)(6)/PPI (b)(6)/PPI (b)(6)/PPI (b)(6)/PPI

Through: (b)(6)/PPI (b)(6)/PPI (b)(6)/PPI (b)(6)/PPI (b)(6)/PPI

Date: December 16, 2021

Subject: Mifeprex Citizen Petition: (Docket No. FDA-2019-P-1534)

Introduction:

The (b)(6)/PPI ((b)(6)/PPI requested that the (b)(6)/PPI ((b)(6)/PPI provide a consult on a Citizen Petition submitted on March 29, 2019, to the Food and Drug Administration (FDA or the Agency) by the American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG) and the American College of Pediatricians (ACPeds). The Petitioners 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.

Background:

On September 28, 2000, Mifeprex 600 mg, followed in two days by 400 mcg oral misoprostol, was approved for medical termination of pregnancy through 49 days' gestation under Subpart H (21 CFR 314.520).[1] Mifeprex was approved with a restricted distribution plan that included a requirement that Mifeprex be provided only by or under the supervision of a physician who met certain qualifications, including the ability to date pregnancy, to identify an ectopic pregnancy, and to provide (directly or through other qualified physicians) surgical intervention in cases of incomplete abortion or severe bleeding. In 2007, with the passage of the FDA Amendment Act, Mifeprex was included among the products deemed to have in effect an approved Risk Evaluation and Mitigation Strategy (REMS) under Section 505-1 of the Federal Food, Drug, and Cosmetic Act. A formal REMS proposal was submitted and the REMS with Elements to Assure Safe Use (ETASU), along with an implementation system and Medication Guide, was approved on June 8, 2011 under Supplement-014. The goals and elements of the REMS are summarized in Table 1 below.

[1] NDA approval letter, Mifeprex (NDA 020687, dated September 28, 2000).

Exhibit 18

Table 1. Summary of Mifeprex REMS Approved in 2011[2]

REMS Goals	To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
	To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications.
REMS Elements	Medication Guide
	ETASU A – Special certification of healthcare providers (HPCs) who prescribe Mifeprex: Completion of Prescriber's Agreement form and enrollment in the REMS program.
	ETASU C – Mifeprex is dispensed only in certain healthcare settings: It is only available to be dispensed in clinics, medical offices or hospitals, under the supervision of a specially certified prescriber. Mifeprex will not be distributed to or dispensed through retail pharmacies.
	ETASU D – Safe-use conditions: Patients must complete and sign the Patient Agreement form that is to be placed in the patient's medical record. A copy of the Patient Agreement form and Medical Guide must be provided to the patient.
Implementation System	Distributors of Mifeprex must be certified and agree to ship Mifeprex only to locations identified by certified prescribers. Distributors must agree to maintain secure and confidential records, as well as, follow all distribution guidelines concerning storage, shipments and controlled returns.

On March 29, 2016, Supplement-020 (S-020) was approved, providing for labeling changes, including but are not limited to the following:

- Extended the maximum gestational age eligible for medical termination from 49 to 70 days' gestation;
- Revised the dosing and dosing regimen: from 600 mg Mifeprex (Day 1, single oral dose)/400 mcg misoprostol (Day 3, single oral dose) to 200 mg Mifeprex (Day 1, single oral dose)/800 mcg misoprostol (Day 2 or 3, by buccal route, 24-48 hours after taking Mifeprex);
- Reduced the required office visits by the patient from three to one (post-treatment assessment Day 7 to 14) to confirm complete termination pregnancy and to evaluate the degree of bleeding.

The consult request from (b)(6)/PPI included 17 questions overall. Among these, (b)(6)/PPI seeks input from (b)(6)/PPI on Questions 1 (parts a and b), 2, 3, 4, 5 (parts a through h), 6, 10, 11, 12, 13 (a, b, and c), 14 (parts a and b), 15, 16, and 17. (b)(6)/PPI responses to (b)(6)/PPI follow in the sections below.

[2] Source: The (b)(6)/PPI REMS Modification Review (NDA 02867/S-020, dated March 29, 2016), Table 1.

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 document, our discussions in this document apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. 355-1(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 document refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

1. Mifeprex Regimen and Prescriber Requirements

A. Indications and Usage:

(b)(6)/ PPI **Question 1.** Citing a 2011 study and a statement by the American College of Obstetricians and Gynecologists (ACOG), Petitioners state that drug-induced abortion regimens demonstrate an increase in complications, including serious risks of failure, hemorrhage, infection and ongoing pregnancy after 49 days gestation (Petition at 3-4). Do you agree? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 1:**
No, we do not agree. The Petitioners' reference of these two publications appears misleading; by quoting sentences from the publications out of context.

The Mentula publication reported old data (2003-2006); we conducted an extensive review of more recent data for our 2016 review of S-020. The Petitioners cite Mentula, et al.,[3] a register-based, retrospective cohort study that included 18,248 women in Finland who

[3] 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.

underwent medical abortion[4] between January 1, 2003 and December 31, 2006. In Finland, medical abortion is permitted up to 20 weeks of gestation or up to 24 weeks of gestation in cases of a confirmed medical condition in the fetus. Mentula et al. was primarily designed to compare immediate adverse events following medical abortion in second trimester (13 to 24 weeks as defined by the authors) to first trimester (up to 12 gestational weeks as defined by the authors). This study was not designed to compare rates of complications, such as serious risks of failure, hemorrhage, infection and ongoing pregnancy, following medical abortion regimens taken before and after 49 days of gestation. The Mentula publication presents the percentages of surgical evacuation following medical abortion and of infection following medical abortion from 2003 to 2006,[5] based on weekly gestational age, from ≥ 5 weeks to ≤ 20 weeks gestation in two figures (Figure 2, and Figure 3, respectively). Although the point estimates for the surgical evacuation rate appear to be increasing for gestational ages weeks 7 to 10, we cannot conclude that the actual surgical evacuation rate at each gestational age (from weeks 7 to 10) differ because the associated 95% confidence intervals for the surgical evaluation rate at each gestational age (weeks 7 to 10) are overlapping. For the same reason, although the point estimates for the infection rate appear to increase for gestational ages 7 to 10, we cannot conclude that the actual infection rate at each gestational age from weeks 7 to 10 differ. Therefore, it is problematic to rely on the rates of complications as reported in the publication to determine whether complications increased by week in pregnancies < 10 weeks. In the Agency's 2016 review of the S-020 efficacy supplement, we reviewed more recent data,[6] and concluded that, Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation. Regardless, serious adverse events through 70 days GA are infrequent per current Mifeprex labeling (Table 2: transfusion 0-0.1%, sepsis < 0.01%, hospitalization related to medical abortion 0-0.7%, hemorrhage 0.1%).

The Petitioners also cite 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."[7,8] This statement is based on a 1998 publication which evaluated women undergoing medical abortion with mifepristone 600 mg and oral

[4] 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.
[5] Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of completion abortion 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."
[6] Cross-Discipline Team Leader Review (b)(6)/PPI) for NDA 20687 S-020, dated March 29, 2016. Table 4: Summary Table of Studies Supporting NDA 20-687 S-020 in Appendix (p 36 of 60).
[7] Medical Management of First-Trimester Abortion. ACOG Practice Bulletin No. 143. March 2014 (Reaffirmed 2016). The quote appears on page 680.
[8] Medication Abortion Up to 70 Days of Gestation. ACOG Practice Bulletin No. 225. October 2020. We note that ACOG Practice Bulletin No. 225 has replaced Practice Bulletin No. 143.

misoprostol 400 mcg two days later.[9] The regimen studied in this 1998 publication is not the currently approved regimen in the United States. We note that ACOG Practice Bulletin No. 143 has been replaced by Practice Bulletin No. 225; the statement quoted by the Petitioners does not appear in ACOG Practice Bulletin No. 225.

(b)(6)/ PPI **Question 1a.** Citing a 2015 meta-analysis, Petitioners state that the failure rate of the buccal misoprostol regimen increased as the gestational age increased, especially at gestational ages greater than 49 days (Petition at 3-4). Do you agree? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 1a:**

We agree that failure rate of medical abortion regimens, including the buccal misoprostol regimen, generally increases with increasing GA. However, the increase in failure rate with each incremental week described in approved mifepristone labeling and in the 2015 meta-analysis discussed below is small and that the benefit/risk profile for medical termination of intrauterine pregnancies between 49 days and 70 days' gestation remains acceptable.

The Petitioners cite a 2015 meta-analysis by Chen and Creinin,[10] which included 20 studies with a total of 33,846 women undergoing medical abortion through 70 days of gestation using the buccal misoprostol regimen. The authors report efficacy (i.e., complete medical abortion rates) of the buccal misoprostol regimen by GA as shown in table below: 98.1% for ≤ 49 days, 96.7% for 50-56 days, 95.2% for 57-63 days, and 93.1% for 64-70 days. These completion rates are consistent with the outcome by GA described in the approved labeling.

	Successful Abortion			Ongoing Pregnancy		
	No. in Analysis	No. Successful	% (95% CI)	No. in Analysis	No. of Ongoing Pregnancies	% (95% CI)
Overall						
Through 63 d of gestation	33,514	32,394	96.7 (96.5–96.8)	32,479	252	0.8 (0.7–0.9)
Through 70 d of gestation	33,846	32,703	96.6 (96.4–96.8)	32,785	261	0.8 (0.7–0.9)
By gestational age (d)*						
49 or less	12,555	12,318	98.1 (97.9–98.3)	10,781	40	0.4 (0.3–0.5)
50–56	4,161	4,024	96.7 (96.1–97.2)	4,008	34	0.8 (0.6–1.2)
57–63	2,202	2,096	95.2 (94.2–96.0)	2,119	39	1.8 (1.3–2.5)
64–70	332	309	93.1 (89.6–95.5)	306	9	2.9 (1.4–5.7)

CI, confidence interval.
All outcomes are based on patients for whom outcome was determined (patients without follow-up are not included).
* Not all studies reported outcome within each specific gestational age range; outcomes are calculated using only those studies with outcome data presented by gestational age.

Source: Table 1, Chen and Creinin 2015.

[9] 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.
[10] Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. Obstet Gynecol. 2015;126(1):12-21.

(b)(6)/ PPI **Question 1b.** Petitioners state that the gestational limit for the Mifeprex regimen should not have been increased (Petition at 4). Do you agree? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 1b:**
No, we do not agree. The (b)(6)/PPI review of S-020 concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancies through 70 days' gestation.[11]

With respect to efficacy, complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of original Mifeprex (mifepristone followed by oral misoprostol regimen through 49 days of gestation) were 92.1 and 95.5% in the US and French trials, respectively. The studies reviewed in support of the 2016 approval (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 clinical review 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 now-approved regimen.[11] The ranges of complete medical abortion rates calculated by the clinical reviewer were: 93.2 to 98.7% in the US studies and 92 to 98.2%in the non-US studies. The Division's 2016 action to extend the GA limit for Mifeprex did not compromise on efficacy.

As discussed above, the rate of serious adverse events through 70 days GA are rare. The benefit/risk assessment supported the Division's 2016 approval.

B. Dosage and Administration:

(b)(6)/ PPI **Question 2.** Do you agree with Petitioners' statement that FDA should limit the ability to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than healthcare providers, 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 3)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 2:**
No, we do not agree. Prior to approval of S-20, the Prescriber's Agreement in the REMS specified that "…Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications…" However, the labeling also stated that other healthcare providers (HCPs), acting under the supervision of a qualified physician, may also dispense/administer Mifeprex to patients. Therefore, the provisions of the labeling (including REMS) approved in 2016 that relate to provider training and admitting privileges are substantially similar to the labeling provisions approved in 2000. Under currently approved labeling, HCPs who administer Mifeprex must be licensed to prescribe, and must have the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These HCPs must

[11] 2016 Medical Review, Table 3 (U.S. studies) and Table 4 (international studies), page 29 and 30 of 100. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf.

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.

As we determined, in conjunction with the (b)(6)/PPI during the review of S-020, the safety and efficacy of allowing non-physician HCPs to order, dispense, and administer Mifeprex are supported by available data. (b)(6)/PPI 2016 review[12] included three randomized clinical trials and one comparative study that evaluated safety and efficacy of medical abortion when performed by non-physician HCPs. Two trials evaluated the Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner),[13,14] one trial studied the regimen using vaginal misoprostol (Warriner),[15] and the fourth study did not specify the route of misoprostol administered (Puri).[16] Olavarrieta reported completion rate of 97.9% when medical abortion was provided by nurses as compared with 98.4% with physicians. Kopp Kallner reported completion rate of 99% with certified nurse midwives vs. 97.4% with physicians. Warriner reported abortion complete rate of 97.4% with nurses as compared with 96.3% with physicians. Puri reported abortion completion rate of 96.8% when the service was provided by nurse-midwives as compared with 97.4% in the "standard care" group. Our 2016 clinical review also included a systemic review of six controlled clinical studies by Renner;[17] 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.[18] This Cochrane review concluded that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors; this conclusion was based in part on the same studies that FDA reviewed in 2016.[19]

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[12] Cross-Discipline Team Leader memorandum, S-020.
[13] 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.
[14] 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 randomized controlled equivalence trial. BJOG. 2015; 122: 510-517.
[15] 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.
[16] 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.
[17] 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.
[18] Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). Cochran Database of Systematic Reviews. 2015, Issue 7.
[19] Of the medical abortion studies reviewed by Barnard et al., two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al. and Kopp Kallner et al. The third study used a different

With respect to identification of patients with contraindications to using Mifeprex, (b)(6)/PPI finds that this evaluation can be done by mid-level HCPs as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass
- 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 prophyrias

The contraindications can be assessed by trained HCP who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. (b)(6)/PPI maintains that HCPs who prescribe possess the clinical and counseling skills necessary to provide medical abortion. Allowing trained advanced practice clinicians to provide medical abortion is supported by ACOG.[20] Furthermore, if necessary, ultrasound training and certification is available to nurse practitioners, physician assistants, as well as physicians (American Institute of Ultrasound in Medicine)[21].

(b)(6)/PPI **Question 3.** Do you agree with Petitioners' statement 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)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/PPI **Question 3:**
No, we do not agree. We refer to FDA's 2016 Denial Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (hereafter referred to as the 2016 CP denial response), where FDA stated that the determination of gestational age does not always require an ultrasound.[22] In the 2016 CP denial response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of

dose of misoprostol than the currently approved regimen. (See Jejeebhoy SJ, 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).

[20] ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. Obstetrics and Gynecology 2020; 136(4); e31 to e47.

[21] American Institute of Ultrasound in Medicine. Accessed November 26, 2021. https://www.aium.org/officialStatements/70

[22] FDA's citizen petition denial response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists on August 20, 2002, Docket No. FDA-2002-P-0364.

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."

(b)(6)/ PPI **Question 4.** Referencing the Provider Agreement Form and the requirements that a provider: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed, Petitioners state that FDA should require certified prescribers to be physically present, rather than consulting with the patient over the Internet, when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4)? Do you agree? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 4:**

No, we do not agree. The certified prescriber does not have to be physically present as long as he/she has evaluated the patient's data which confirm a patient's gestational age and intrauterine pregnancy and rule out contraindications as listed and discussed in our response to Question 2 above. As noted above, in the 2016 CP denial response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."[23] A certified prescriber can also review the Patient Agreement Form[24] with the patient, fully explain the risk of the Mifeprex treatment regimen, and answer any questions, as with any consent process, without physical proximity. To address requirement (3), the certified prescriber must provide or arrange to provide emergency intervention through others and to assure patient access to appropriate medical facilities. It is common practice for HCPs to provide emergency care coverage for other HCPs' patients and in many places, hospitals employ "hospitalists" to provide care to all patients. We also note ACOG's statement that if women need access to emergency surgical intervention, "it is medically appropriate to provide referral to another HCP if needed."[25]

(b)(6)/ PPI **Question 5**. Do you agree with Petitioners' statement that the use of Mifeprex and misoprostol should require three office visits by the patient (Petition at 7)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 5:**

No, we do not agree. See also our response to (b)(6)/ PPI Question 4.

The safe use of Mifeprex for medical abortion is not contingent on a specific number of office visits made by the patient undergoing medical abortion. We concluded, upon

[23] Id.
[24] Mifeprex REMS https://www.accessdata fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf
[25] ACOG Practice Bulletin No. 225. Mediation Abortion Up to 70 Days of Gestation. Obstetrics and Gynecology 2020; 136(4); e31 to e47.

reviewing the data in S-020, that the elements necessary to assure the safe use of Mifeprex could be scaled back to offset the burden on the patients.[26] These elements include:

- Requiring that healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS program;
- Ensuring that Mifeprex is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber;
- Informing patients about the risk of serious complications associated with Mifeprex.

We do not consider three office visits are necessary to satisfy these elements. The previously required Day 3 visit, mandating administration of misoprostol in clinic, was especially burdensome, considering that most patients will expel the pregnancy within 2 to 24 hours of taking misoprostol.

(b)(6)/ PPI **Question 5a.** Do you agree with Petitioner's statement that providers may now "confirm" that a patient's drug-induced abortion was successful without a clinic visit (Petition at 7)? Please explain why or why not?

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 5a:**
The 2016 Mifeprex labeling states that complete pregnancy termination "can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasound scan." Not all these modalities require an in-clinic assessment. The 2016 labeling change regarding post-treatment assessment (from specifying an in-office assessment on Day 14 to advising that patients should follow-up with their HCP approximately 7-14 days after taking Mifeprex and not specifying what assessment should be performed) was based on evidence reviewed in S-020. FDA's review concluded that "available data support … that there are a variety of follow-up modalities that can adequately identify the need for additional intervention."[27] These findings are also consistent with ACOG guidelines, which state that "an in-clinic evaluation is not always necessary" and recommends several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at 1 week after treatment followed by urine pregnancy testing at 4 weeks after treatment.[7] Because there is more than one effective option to detect an on-going pregnancy, we conclude that how post-treatment follow-up is performed may be determined by the HCP and the patient.

[26] 2016 Clinical Review. supra n. 44 and 64-67.
[27] 2016 Cross Discipline Team Leader Review
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf. p17/60

(b)(6)/ PPI **Question 5b**. Do you agree with Petitioners' statement that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex and that home administration of misoprostol does not permit the health providers to control when women take the misoprostol (Petition at 7)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 5b:**
During our review for S-020, the evaluation of home use of misoprostol included over 30,000 women. The data showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective.[28] Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. Additionally, 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.

(b)(6)/ PPI **Question 5c.** Do you agree with Petitioners' statement that: (1) the use of buccal misoprostol sooner than 24 hours of administering mifepristone leads to significantly increased failure rates; (2) oral administration of misoprostol is not as effective in ending the pregnancy; (3) taking misoprostol earlier than 48 hours after Mifeprex is more likely to "fail the regimen (Petition at 7)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 5c:**
Incorrect self-administration of medication has not been shown to adversely affect efficacy and safety (see (b)(6)/PPI response to (b)(6)/ PPI Question 5b above).

The Petitioners state the use of buccal misoprostol sooner than 24 hours of administering mifepristone leads to a significantly increased failure rate and cites a pilot study by Lohr et al.[29] Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (≤ 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations[30,31] using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates at 24 hours reported by Lohr for oral mifepristone and buccal misoprostol were 72.5%, 69.2%, and 72.5%,

[28] 2016 Clinical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf. page 41.
[29] 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.
[30] 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.
[31] 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.

respectively, for the three gestational age groupings. The complete abortion rates at 2 weeks reported by Lohr for oral mifepristone and buccal misoprostol were 97.5%, 100%, and 94.9%, respectively. The published complete abortion rates at 24 hours for oral mifepristone and vaginal misoprostol were 90%, 88%, and 83%, respectively, for gestational age groupings and the complete abortion rates at 2 weeks for oral mifepristone and vaginal misoprostol were 98%, 93%, 90% respectively.[32,33] As recommended in Section 2.3 of approved labeling, follow-up at the 7-14 day after administration of mifepristone is more appropriate to evaluate efficacy. Based on the data presented in Lohr, the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. In Section 2.1 Dosing Regimen in labeling, we advise women to take misoprostol within 24 to 48 hours after taking mifepristone. While we acknowledge that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration, we do not agree that doing so would result in a significantly increased failure rate.

The Petitioners are concerned that self-administration of misoprostol may result in swallowing rather than buccal administration with resultant decreased efficacy. Winikoff et al. specifically studied the use of oral vs buccal misoprostol 24-36 hours after mifepristone 200 mg in women with pregnancies up to 63 days with overall medical abortion success rates of 91.3% vs 96.2%.[34] Although the study showed decreased efficacy with oral vs. buccal misoprostol in 57-63 days gestational age (85.1% versus 94.8%), there were no statistical differences in other gestational age groupings. 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. As we note above in our response to Question 1b, our 2016 review included 22 studies which assessed mifepristone 200 mg followed in 24 to 48 hours by buccal misoprostol in pregnancies through 70 days gestation. As stated above, the ranges of complete medical abortion rates reported were: 93.2 to 98.7% in the US studies and 92 to 98.2% in the non-US studies.

The Petitioners cite the 2015 systematic review by Chen and Creinin. The Petitioners state that the review found "women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen." 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

[32] Id.
[33] Schreiber CA, supra n. 31
[34] 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.

with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2% compared with compared with 96.8%)."[7] The differences in efficacy rates were statistically significant but both regimens are more effective than the 92% efficacy rate of the original FDA-approved regimen. In the 2016 clinical review, we stated that "[p]recise timing of the administration of misoprostol has not been shown to result in a higher success rate which is why the majority of the [22 studies reviewed] allowed a range of hours between the mifepristone dose and misoprostol dose rather than one set time between [mifepristone and misoprostol]."[35] Our 2016 review also referenced a 2013 systematic review by Raymond, which concluded that "if mifepristone-misoprostol interval is < 24 hours, the procedure is less effective compared to an interval of 24-48 hours."[36] Therefore, under Section 2 Dosing Regimen, the labeling approved in 2016 recommends a "minimum 24-hour interval between" mifepristone and misoprostol (underline emphasis included in the labeling).

(b)(6)/ PPI **Question 5d**. In support of Petitioners' assertion that more healthcare oversight is needed, the Petitioners cite the World Health Organization's finding that up to 90% of women will abort with 4-6 hours after taking misoprostol and under the 2000 regimen patients were permitted to remain in the clinic during this time-period (Petition at 8). The Petitioners also cite a 2018 study to support the Petitioners' statement that abortion complications are more frequent when women aborted at home (Petition at 8). Do you agree? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 5d:**

No, we do not agree. The Petitioners appear to cite the WHO guidance document out of context. In stating that up to 90% of women will expel the products of conception (i.e., abort) within 4-6 hours after taking misoprostol, the WHO guidance states so in the context of recommending adequate pain management because most women are likely to require medication for cramping pain during this time period.[37] The WHO guidance takes no position in whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol. In fact, the WHO guidance explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.[38] In the U.S., and as reflected in the approved labeling, medical abortion usually involves women terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

[35] 2106 Medical Review, supra n. 11, at 31

[36] Id.

[37] 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.

[38] Id. at Section 2.3 Post-abortion care and follow-up, page 52.

The Petitioners also cite Carlsson, et al., a study that evaluated complications following all medical and abortions (both less than 12 weeks and more than 12 weeks) as well as surgical abortions performed at one hospital in Sweden between 2008 and 2015.[39] For the years 2008 to 2010, data were collected retrospectively; for the years 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 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 appear similar for the "at home" group (10.0 percent) and the "at the hospital" group (9.3 percent).

Notably, our 2016 clinical review 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 with the [regimen approved in 2016] are rarely reported 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.[40]

In summary, the totality of data on the safety and efficacy of medical abortion less than 70 days gestation derived from numerous studies has characterized the complications and rates of complications for completing medical abortion at home with the findings showing medical abortion at home is both safe and effective.

(b)(6)/ PPI **Question 5e**. Do you agree with Petitioners' statement that a follow-up examination is particularly critical for Rh-negative patients and without the follow-up, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 5e:**
No, we do not agree. The Petitioners 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. Rh testing is standard of care in the U.S. and RhD immunoglobulin (such as Rhogam) should be

[39] 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.
[40] 2016 Medical Review, pages 51 to 57 of 100.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf.

administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).[41] However, at what facility (clinic, hospital, laboratory) the Rhogam injection occurs is not critical. A shift from medical clinics to hospitals for administration of Rhogam injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.[42] This has resulted in pregnant women obtaining the routine 28-week Rhogam injection at hospitals/laboratories with a prescription provided by their HCPs. This same process of obtaining RhD immunoglobulin via prescription is available to women after medical abortion and does not require a follow-up clinic visit.

(b)(6)/ PPI **Question 5f**. Do you agree with Petitioners' representation of the cited studies regarding the reduction of required visits (Petition at 9-10)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 5f:**

Yes, we agree. The three studies referenced[43,44,45] evaluate the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies after medical abortion and the ability of women to self-administer and interpret the test results. The studies overall conclude that in the majority of women, it is feasible to use a simplified test to determine whether further follow-up is necessary. We acknowledge that urine pregnancy tests are used for post medical abortion follow up. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion using a low sensitivity or semiquantitative urine pregnancy test with or without symptom check list completed at home. At home self-assessment compared with routine clinic follow up after medical abortion was not inferior to routine clinic follow up.[46] Recent ACOG recommendations indicate 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."[47] Nonetheless, the FDA-approved label for mifepristone states patients should follow up

[41] ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.
[42] https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers
[43] Lynd K, Blum J, Thi Nhu Ngoc N, et al., 2013, Simplified Medical Abortion Using A Semi-Quantitative Pregnancy Test for Home-Based Follow-Up, Internal Journal of Gynecology and Obstetrics, 121:144-148.
[44] Raymond, E, Tan, Y, Grant, M, et al., 2018, Self-Assessment of Medical Abortion Outcome Using Symptoms and Home Pregnancy Testing, Contraception 97:324-328.
[45] Raymond E, Shochet T, Bracken, H, 2018, Low-Sensitivity Urine Pregnancy Testing to Assess Medical Abortion Outcome: A Systematic Review, Contraception 98:30-35.
[46] 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.
[47] ACOG Practice Bulletin Number 225, Medication Abortion Up to 70 Days of Gestation. Obstetrics Gynecol 2020;136(4): e31-e47.

with their healthcare provider approximately 7-14 days after administration of misoprostol to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, hCG testing or ultrasonographic scan.
The Petitioners note in one study[48], 26% of participants provided no follow up information. We also note that this level of lack of follow up information is not uncommon in similar studies.

(b)(6)/ PPI **Question 5g**. Do you agree with Petitioners' statement that ACOG acknowledges that drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 5g:**
No, we do not agree. As discussed in our response to (b)(6)/ PPI Question 5a, post-medical abortion follow-up may be accomplished in many ways and not all require an in-clinic visit. ACOG states that "Women are not good candidates for medical abortion if they …are not available for follow-up contact or evaluation…" and notes that medical abortion requires follow-up to ensure completion of abortion.[4] Neither of these statements contraindicates medical abortion in women who are not available for an in-clinic follow-up visit. Rather, ACOG's statements may be considered by the women and their HPCs in the consultation and consent process to determine the best abortion option for each woman.

(b)(6)/ PPI **Question 5h**. Do you agree with Petitioners' statement that drug-induced abortion is a longer process that requires more attention and care from HCPs (Petition at 10)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 5h:**
We agree that medical abortion can be a longer process than surgical abortion[49] but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. None of the complications associated with medical abortion necessarily requires more intensive management from HCPs 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 women who are appropriate candidates. Contrary to what the Petitioners claim,

[48] Raymond, supra n.44
[49] See ACOG Practice Bulletin Number 225, supra n. 26.

reducing the number of clinic visits does not compromise patient safety and is not done for the "convenience" of healthcare providers or patients.

C. Contraindications:

(b)(6)/ PPI **Question 6**. Petitioners note that critical language contraindicating Mifeprex for patients without access to appropriate medical care was excluded from the 2016 Mifeprex label and cite a study and ACOG statements indicating that Mifeprex abortions have greater risks and more need for emergency reoperation than a surgical abortion. Petitioners focus on this point particularly for patients in rural areas with limited access to emergency medical care (Petition at 11). Do you agree? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 6:**

No, we do not agree. The 2016 labeling is consistent with the 2006 Physician Labeling Rule (PLR) format, which includes a Boxed Warning and lists the Mifeprex REMS program which was established after the 2000 approval.

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in Section 4 of the approved labeling, the 2016 labeling continue to include appropriate instructions for providers regarding patient access to appropriate medical care in the designated sections of Mifeprex labeling as seen below:[50] (underline added)

- Boxed Warning: Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol.
- 2.2 Patient Management Following Misoprostol Administration
  Give the patient:… The name and phone number of the healthcare provider who will be handling emergencies.
- 17 Patient Counseling Information
  Provider Contacts and Actions in Case of Complications
  Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, or if she experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever [see Boxed Warning].

[50] Mifeprex labeling, approved 2016.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf

Additionally, one of the required qualifications listed in the Prescriber Agreement Form is "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."[51]

The Petitioners cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.[4] We note that Practice Bulletin No. 143 is no longer in effect and has been replaced by ACOG Practice Bulletin No. 225, which does not have language contrasting the features of medical and surgical abortion.

D. Adverse Event Reporting:

(b)(6)/PPI **Question 7.** Do you agree with Petitioners' statement that collecting accurate and complete adverse event information for Mifeprex is highly difficult and that many prescribers violate FDA protocol and instruct their patients to lie to emergency medical personnel (Petition at 12)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/PPI **Question 7:**
No, we do not agree. The safety profile of Mifeprex with misoprostol for medical abortion is well-established based on clinical studies performed over several years. Since the approval in 2000, no new safety concerns have arisen and the known serious risks occur infrequently (< 0.7%). FDA routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all other application holders, the Applicant is required 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. In addition to this requirement for the NDA holder(s), certified physicians are required to report any deaths.

We cannot address the Petitioners' accusation that many Mifeprex prescribers instruct their patient to lie to emergency medical personnel because we have no documentation that U.S. prescribers instruct their patients to lie. The Petitioners cite instructions from the organization Aid Access to patients that they could tell emergency room staff that they had a miscarriage. We note that Aid Access facilitates the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA has sent Aid Access a letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers.[52]

We recommend that (b)(6)/PPI also seeks input from the (b)(6)/PPI and the (b)(6)/PPI in the (b)(6)/PPI

[51] Mifeprex REMS, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf. Prescriber Agreement starts on page 6.
[52] US FDA Warning Letter to Aid Access.org, dated March 8, 2019. https://www fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019

(b)(6)/PPI **Question 10**. Do you agree with Petitioners' statement that FDA should provide guidance to emergency healthcare providers and physicians so they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/PPI **Question 10:**
No, we do not agree. The FDA has worked with the NDA holder to issue several communications to HCPs and emergency department providers advising an "elevated index of suspicion" for serious adverse events such infection and sepsis following medical abortion. These communications can be located on the webpage Historical Information on Mifepristone (marketed as Mifeprex) and include, but not limited to, the following:

- November 15, 2004: Dear Health Professional Letter and Dear Emergency Room Director Letter
- July 19, 2005: Healthcare Professional Sheet, Public Health Advisory, and revised labeling
- March 17, 2006: Public Health Advisory
- February 24, 2010: Mifeprex Questions and Answers

Since the issuance of these communications, we have not identified a change in the safety profile of mifepristone.[53] Our assessment is also supported by ACOG's Committee Opinion Number 427, which discusses complications to abortion (spontaneous or induced) and states postabortion care "refers to a specific set of services for women experiencing problems for all types of spontaneous or induced abortions."[54] The care "involves management of incomplete abortion, and complications include retained tissue, hemorrhage, and infection." Because there does not appear to be any specific complications that occur solely in medical abortion, there is no guidance at this time to provide emergency HCPs. Finally, if we become aware of safety information that merits further communications, or that warrants revisions to the approved labeling, we will act as appropriate.

2. Mifeprex REMS

A. Request to Retain Mifeprex REMS:

(b)(6)/PPI **Question 11**. Do you agree with Petitioners that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat

[53] Postmarketing safety reviews (done every six months) by the (b)(6)/PPI dated September 24, 2021, April 12, 2021, October 6, 2020, etc.
[54] Misoprostol for Postabortion Care. ACOG Committee Opinion Number 427. February 2009.

Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/PPI **Question 11:**

No, we do not agree that an additional study is needed. These at-risk populations have been included in clinical trials evaluating medical abortion; they have been found to be appropriate populations for Mifeprex use.

- The Petitioners state that Mifeprex was approved for use in the pediatric population after the requirement for studies in the pediatric population were waived. During the 2016 review for S-20, a partial waiver was granted for pediatric studies in premenarchal females under because pregnancy does not occur in premenarchal females. Additionally, in conjunction with the Agency's (b)(6)/PPI, (b)(6)/PPI concluded that the Applicant had provided adequate information to support efficacy and safety in adolescents aged 12 to 16 years. The totality of this information includes data extrapolated from adults and information in literature.[55] Over 1,000 adolescents aged 12 to 17 years used Mifeprex and misoprostol for medical abortion in the trials evaluated by (b)(6)/PPI Review of these findings found the efficacy and safety in this population to be similar to the efficacy and safety in the adult population.
- Published data concerning adverse reproductive health outcomes in US women who undergo repeat medical abortions with Mifeprex are limited. Our 2016 clinical review stated that "there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect." The review also noted that return to fertility is well-documented: in the Patient Counseling Information section, the labeling states "inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses" and "inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before she resumes sexual intercourse." The Medication Guide also conveys the same information, stating: "You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again." Although the Petitioners state that more than one out of every three abortion in the US is a repeat abortion,[56] (b)(6)/PPI is not aware of reports suggesting greater safety concerns in repeat abortion than first-time abortion. The Petitioners 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.[57] However, these data from a single nonclinical study in mice are not persuasive, given that return to fertility after medical abortion is known clinically;

[55] Primary Clinical Review for S-20, dated March 29, 2016.
[56] 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
[57] Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. PLoS One. 2012;7(10):e48384.

please see our 2016 clinical review. Therefore, we do not agree that a study is necessary in this population.

- The Petitioners request a formal study of mifepristone for medical abortion in women without access to emergency care. However, certified prescribers must attest that they have the 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 the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. Therefore, mifepristone is prescribed only to women who are assured access to emergent care if needed. We do not agree that a study as suggested by the Petitioners is needed.
- In the 2016 review for S-20, (b)(6)/PPI conducted a literature review of self-administration of misoprostol at home. In the clinical trials reviewed, over 30,000 women (including over 13,000 US women) had home use of misoprostol (Table 8 in the clinical review for S-20).[7] (b)(6)/PPI found no efficacy or safety concerns with home self-administration of misoprostol.

(b)(6)/PPI **Question 12**. Citing the Council for International Organizations of Medical Sciences' (CIOMS) definitions[58] of "rare" and a 2018 Swedish study, Petitioners state that because "about 1 out of 100 women" using Mifeprex/misoprostol require surgery, serious complications are common, not rare,[29] and medical abortions carry greater risks than surgical abortions (Petition at 15-16). Do you agree? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/PPI **Question 12:**

No; we do not agree. The Petitioners reference definitions and frequencies of adverse drug reactions from CIOMS[59] and reference two sentences in the Medication Guide that refer to different events. Petitioners state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and 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." Using these two separate statements in the Medication Guide, the Petitioners 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. However, the Petitioners' reference to these two statements conflate two different clinical scenarios: (1) the adverse events of serious and potentially life-threatening bleeding, and (2) treatment failure. The first sentence (under section What symptoms should I be concerned with) states: "Although cramping and

[58] https://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf

[59] 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.

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 problems that can occur during expulsion of a pregnancy regardless of gestational age or mode of delivery (e.g., vaginal delivery or cesarean section). During the 2016 Mifeprex review, the reported rate of death in the submitted studies reviewed by the FDA, based on one death, was 0.007% (very rare by CIOMS), the rate of infections requiring hospitalization or intravenous antibiotics was < 0.1% (rare by CIOMS), and the rate of transfusion were 0.03-0.7% (rare to uncommon by CIOMS).[60] Therefore, "rarely" accurately refers to the frequency of the adverse events referenced in this statement. The second sentence (under section Be sure to contact your healthcare provider promptly if you have any of the following; subsection Heavy Bleeding): "In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C)." This statement refers to the rate of surgical procedures for bleeding that occurred in women 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.

The Petitioners cite a Niinimaki, et al.[61] study reporting 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. The overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0% vs. 5.6%). Specifically, hemorrhage (15.6% vs. 2.1%), incomplete abortion (6.7% vs. 1.6%), and surgical (re)evacuation (5.9% vs. 1.8%) were higher for medical abortion compared with surgical abortion. However, injuries requiring operative treatment or operative complications were higher in the surgical abortion group (0.6% vs. 0.03%). No differences were noted in the incidence of infections, thromboembolic disease, psychiatric morbidity, or death. The authors acknowledged weaknesses in registry data, including variable reliability of diagnoses and severity of diagnoses. They stated that there was a high rate of consultation for the diagnosis of hemorrhage, which was not surprising because medical abortion is associated with uterine bleeding lasting approximately two weeks and specifically noted that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after

[60] These rates are reported in Section 6 (Adverse Reactions) of the approved mifepristone labeling.
[61] 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.

termination of pregnancy. The incidence of such bleeding was relatively low, but it was more common in the medical abortion group (2.9% vs. 0.9%). The authors concluded that both methods are generally safe; they recommend discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination. Ireland, et al.[62] reported findings from a more recent retrospective cohort study of 30,146 US women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6% and 99.8% for medical and surgical abortion, respectively, which represented a fourfold higher risk of abortion failure in those undergoing medical abortion. Unanticipated aspiration for persistent pain, bleeding or both were 1.8% and 0.4% for medical and surgical abortion respectively. These findings are compatible with the Niinimaki study findings. There was no difference in major adverse events (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.

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical evacuation, but without increases in major adverse events (e.g., death, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion). However, in a vast majority of medical abortions, surgical intervention can be avoided. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. It should be up to women and their HCPs to decide which method is preferable and safer according to each woman's unique situation.

(b)(6)/ PPI **Question 13.** Do you agree with Petitioners' representation of the cited studies on the use of mifepristone for management of early miscarriages (Petition at 16-17)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 13:**

The use of mifepristone for the management of early miscarriages is investigational and outside the scope of the Mifepristone REMS Program.

(b)(6)/ PPI **Question 13a:** Do you agree with Petitioners' statement that the Mifeprex + misoprostol arm raises concerns about the need for further study of adverse events, especially hemorrhage (Petition at 17)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 13a:**

[62] 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.

Please see our response to (b)(6)/PPI Question 13. The use of mifepristone for the management of early miscarriages is investigational and outside the scope of the Mifepristone REMS Program.

(b)(6)/PPI **Question 13b:** Do you agree with Petitioners' statements that use of mifepristone to manage spontaneous miscarriages ignores: (1) clear methodological errors, including a failure to accurately diagnose fetal death according to accepted criteria as well as a lack of adherence to the stated inclusion criteria, and (2) the absence of power to evaluate safety (Petition at 18)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/PPI **Question 13b:**

Please see response to (b)(6)/PPI Question 13.

(b)(6)/PPI **Question 13c.** Do you agree with Petitioners' statement that a change in spontaneous miscarriage management using mifepristone should require a new drug application with two randomized controlled trials comparing the arms of mifepristone and misoprostol, misoprostol alone, surgical management and expectant management (Petition at 18)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/PPI **Question 13c:**

Whether the clinical programs pursuing the management of miscarriage indication are adequate is outside the scope of the Mifepristone REMS Program.

B. Request to Continue Dispensing Limitations of Mifeprex:

(b)(6)/PPI **Question 14.** Do you agree with Petitioners' statement that eliminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls and that healthcare 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)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/PPI **Question 14:**

The current mifepristone labeling states that 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 prescribers. We do not agree that eliminating the REMS requirement for the dispensing of mifepristone in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of HCPs to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. Evaluation, consent, development of a follow-up plan, and contact for emergency care can occur in many types of healthcare settings. The evaluation of women for contraindications to medical

abortion includes assessment of medical history and clinical examination (e.g., physical examination or ultrasound examination); these do not necessarily require physical contact with a certified prescriber (see response to (b)(6)/ PPI Question 2).[15]

Patients who are not pregnant at the time of evaluation would not be appropriate candidates for Mifepristone dispensation because they do not fulfill the indication of having an intrauterine pregnancy through 70 days gestation.

See also REMS Modification Rationale Review Memorandum dated December 16, 2021, which provides the (b)(6)/PPI and the (b)(6)/PPI rationale and recommendations for modifications to the Mifepristone REMS Program for NDA 020687 and ANDA 091178.[63]

(b)(6)/ PPI **Question 14a.** Do you agree with Petitioners' statement that without direct patient contact, Rh-negative patients will not receive the Rhogam after their abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 19)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 14a:**

No, we do not agree; see our response to Question 5e. "Direct patient contact" with a certified prescriber is not necessary for the administration of Rhogam in Rh-negative women. Further, many women must obtain Rhogam injections from local hospitals with an HCP prescription due to Rhogam shortages and reimbursement from third-party payers.

(b)(6)/ PPI **Question 14b.** Do you agree with Petitioners' statement that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 14b:**

No, we do not agree. HCPs who prescribe Mifepristone for medical abortion are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the AMA that a physician-patient relationship is entered when the "physician serves a patient's medical needs"[64] and continues until resolution of the pregnancy or transfer of care to another HCP. Further, the following excerpts are taken from the American Medical Association (AMA) Ethical Practice in Telemedicine:

[63] REMS Modification Rationale Review Memorandum dated December 16, 2021 https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af80633d74&_afrRedirect=23032383998405 20

[64] www.ama-assn.org/delivering-care/ethics/patient-physician-relationships

- "Physicians who provide clinical services through telehealth/telemedicine must uphold the standards of professionalism expected in in-person interactions, follow appropriate ethical guidelines of relevant specialty societies and adhere to applicable law governing the practice of telemedicine."
- "Physicians must ensure that they have the information they need to make well-grounded clinical recommendations when they cannot personally conduct a physical examination, such as by having another health care professional at the patient's site conduct the exam or obtaining vital information through remote technologies."
- "When the physician would otherwise be expected to obtain informed consent, tailor the informed consent process to provide information patients (or their surrogates) need about the distinctive features of telehealth/ telemedicine, in addition to information about medical issues and treatment options. Patients and surrogates should have a basic understanding of how telemedicine technologies will be used in care, the limitations of those technologies, the credentials of health care professionals involved, and what will be expected of patients for using these technologies."
- "As in any patient-physician interaction, take steps to promote continuity of care, giving consideration to how information can be preserved and accessible for future episodes of care in keeping with patients' preferences (or the decisions of their surrogates) and how follow-up care can be provided when needed. Physicians should assure themselves how information will be conveyed to the patient's primary care physician when the patient has a primary care physician and to other physicians currently caring for the patient."[65]

(b)(6)/ PPI **Question 15.** Do you agree with Petitioners' representations of a 2018 study, the 2018 Grossman op-ed, and the Guttmacher Institute's 2018 Policy Review, discussing alternative models of providing abortion medications and advocating for the lifting of the REMS on mifepristone (Petitioner at 23-24)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 15:**

Yes. We agree that the overarching message in the publications referenced appears to be advocating self-management of medical abortion. The references, Biggs, et al,[66] Grossman,[67] and a Guttmacher Institute's Policy Review,[68] examine expanding access to medical

[65] https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine
[66] Biggs MA, Ralph L, Raifman S, et al. Support for and interest in alternative models of medication abortion provision among a national probability sample of U.S. women. Contraception. 2019:99:118-124.
[67] Grossman D, November 2, 2018, Op-Ed: American Women Should Have Access to Abortion Pills Before They Need Them, https://www.latimes.com/opinion/op-ed/la-oe-grossman-abortion-pills-20181121-story html
[68] Donovan MK, 2018, Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care, Guttmacher Policy Review, Vol. 21. https://www.guttmacher.org/gpr/2018/10/self-managed-medication-abortion-expanding-available-options-us-abortion-care

abortion. All three discuss removal of the REMS and access to Mifeprex and misoprostol without a prescription. Biggs and the Guttmacher Institute's Policy Review also discuss obstacles to access other than the REMS and the need for a prescription.

Biggs et al presents findings from a survey of a "representative U.S. sample of women" on interest and support and perceived advantages and disadvantages of alternative models of medical abortion.[40] The three alternative models of medical abortion are described with a preface that medical abortion is safe and effective and does not include information on known adverse reactions. Interestingly, perceived disadvantages (incorrect administration, absence of clinician visit, concerns with safety) of the alternative methods were higher than perceived advantages (privacy, convenience, earlier access) in most categories tabulated.

Grossman's op-ed advocates for alternative methods of medical abortion and states the FDA restrictions are medically unnecessary and not consistent with the findings of the Biggs survey. Grossman further opines that advanced provision of drug products for emergency contraception helped in the eventual approval for an over-the-counter switch and suggests a similar pathway could be used for an over-the-counter switch of Mifeprex and misoprostol for medical abortion.

The Guttmacher Institute's Policy Review (entitled Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care) discusses obstacles to providing a full range of safe and effective options for abortion care, including access to a provider if needed or wanted at any stage of the abortion, state restrictions on medical abortions, federal laws allowing physicians and pharmacists to refuse to provide care, stigma and criminalization of self-abortion, and affordability. The Policy Review does note that these obstacles would not be eliminated with the removal of the REMS.

(b)(6)/ PPI **Question 16.** Do you agree with Petitioners' statement that Mifeprex prescribers should continue to be certified as qualified (Petition at 25)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 16:**

Yes. We agree that only qualified HCPs should prescribe or supervise HCP who prescribe Mifeprex. The Mifepristone REMS Program states that prescribers of Mifepristone should have or be under the supervision of a certified HCP who has the ability to assess pregnancy duration accurately, diagnose ectopic pregnancy, provide surgical intervention if needed or have made plans to provide such care through others, and have the ability to assure access to medical facilities equipped to provide blood transfusions and resuscitation, if needed and explain the risks of the Mifepristone treatment regimen including answering any questions. In other words, prescribers of Mifepristone should be able to accurately access eligibility for medical abortion, provide informed consent, and provide follow-up care including treatment of adverse events related to medical abortion.

Please see also response to (b)(6)/ PPI Question 17.

(b)(6)/ PPI **Question 17.** Do you agree with Petitioners' request that FDA retain the Mifeprex REMS (Petition at 14)? Please explain why or why not.

(b)(6)/PPI **Response to** (b)(6)/ PPI **Question 17:**

In 2021, FDA undertook a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1(g)(2)). We agree that FDA should retain the Mifepristone REMS Program. See REMS Modification Rationale Review Memorandum dated December 16, 2021, which provides the (b)(6)/PPI and the (b)(6)/PPI rationale and recommendations for modifications to the Mifepristone REMS Program for NDA 020687 and ANDA 091178.

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/

(b)(6)/PPI

12/16/2021 02:42:15 PM

(b)(6)/PPI

12/16/2021 02:43:17 PM

(b)(6)/PPI

12/16/2021 02:44:43 PM

Exhibit 19

U.S. FOOD & DRUG ADMINISTRATION

ANDA 091178/S-004

PRIOR APPROVAL SUPPLEMENT APPROVAL

GenBioPro, Inc.
(b) (6), (b) (4)

Attention: (b) (6), (b) (4)

Dear Sir or Madam:

This is in reference to your supplemental abbreviated new drug application (sANDA) received for review on June 22, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Mifepristone Tablets, 200 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The sANDA, submitted as "Prior Approval Supplement," provides for modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program. This SSS REMS is known as the Mifepristone REMS Program.

APPROVAL & LABELING

We have completed the review of this sANDA, as amended, and it is **approved**.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

In order to ensure the benefits of Mifepristone Tablets, 200 mg. outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated December 16, 2021. In addition the following modifications were communicated during the course of the review:

- Revisions to the REMS goal to align with the updated REMS requirements.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

Exhibit 19

- 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*).

Your proposed modified REMS, received on June 22, 2022, and amended is approved and will be posted on the FDA REMS website: http://www.fda.gov/rems.

The modified REMS consists of elements to assure safe use and an implementation system.

The modification of the approved REMS must be fully implemented within 120 calendar days of this letter.

Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j) of the FD&C Act. A violation of this provision in 505-1(f) of the FD&C Act could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 091178 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 091178/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR ANDA 091178

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email REMSWebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

If your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts, we remind you that you must comply with the postmarking safety reporting requirements for an approved combination product (21 CFR Part 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

If you have any questions, call (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

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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/

(b) (6)

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