APPENDIX TO PETITIONER STATES' CITIZEN PETITION DATED JUNE 5, 2025[1]

Source	Appendix Starting Page
21 U.S.C. § 355-1(f)(1)(A).	Omitted pursuant to 21 C.F.R. § 10.20(c)(1)
21 U.S.C. § 355-1(f)(2)(A).	Omitted pursuant to 21 C.F.R. § 10.20(c)(1)
21 U.S.C. § 355-1(f)(2)(C).	Omitted pursuant to 21 C.F.R. § 10.20(c)(1)
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 29, 2016
Subject	Summary Review
NDA #/Supplement #	20687/S-020
Applicant name	Danco Laboratories, LLC
Date of submission	May 28, 2015
Date of submission receipt	May 29, 2015
PDUFA goal date	March 29, 2016
Proprietary name/established name	Mifeprex/mifepristone
Dosage form/strength	Oral tablet/200 mg
Dosage regimen	Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol
Proposed indication	Mifeprex is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation
Action	Approval

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

Danco Laboratories, LLC, referred to hereafter as the Applicant, submitted an efficacy supplement (S-020) to NDA 20687 for Mifeprex (mifepristone). The Applicant sought the following changes to its approved application:

1. (b) (4) Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally; see below:
   - Day One: Mifeprex Administration (oral)
     One 200 mg tablet of Mifeprex is taken in a single oral dose
   - After a 24-48 hour interval: Misoprostol Administration (buccal)(minimum 24-hour interval between Mifeprex and misoprostol)
     Four 200 mcg tablets (total dose: 800 mcg) of misoprostol are taken by the buccal route

2. Removal of the instruction that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex
5. Increase in the maximum gestational age from 49 days to 70 days
6. Change of the labeled time for expected expulsion of pregnancy from 4-24 hours to 2-24 hours post misoprostol administration
7. Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change of "physician" to "healthcare provider" in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change in the indication statement to add reference to use of misoprostol: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation."
10. Removal of references to "under Federal law" from the Prescriber's Agreement under the REMS

11. Labeling changes addressing the pediatric requirements under the Pediatric Research Equity Act

This efficacy supplement submission includes information from published studies, review articles and additional information from the authors of some of the publications. These published studies evaluated reproductive age women in the U.S. and outside the U.S. who had early medical termination with mifepristone, in a regimen with misoprostol, including women up through 70 days of gestation.

This memorandum serves as the Division's decisional memorandum for the efficacy supplement.

2. Background

The active ingredient of Mifeprex, mifepristone, is a progestin antagonist. Mifeprex, in a regimen with misoprostol, is approved for the medical termination of pregnancy up through 49 days' gestation. The approved dosing regimen is currently labeled as follows:

- Day 1: The patient takes three 200 mg tablets of Mifeprex in a single oral dose in the clinic, medical office, or hospital.
- Day 3: The patient returns to the clinic, medical office, or hospital and takes two 200 mcg tablets of misoprostol orally.
- Day 14: The patient returns for a follow-up visit to confirm that a complete termination has occurred.

At the time of the September, 2000 approval, FDA restricted distribution of Mifeprex under 21 CFR 314.520, requiring that Mifeprex be dispensed only by or under the supervision of a physician who meets certain qualifications. With the passage of FDAAA in 2007, Mifeprex was deemed to have in effect an approved REMS. The Applicant submitted a formal REMS, which was approved on June 8, 2011 and consisted of the following: a Medication Guide, elements to assure safe use (ETASU A [special certification of healthcare providers who prescribe Mifeprex], ETASU C [dispensing only in certain healthcare settings], and ETASU D [safe use condition of a signed Patient Agreement]), an implementation system and a timetable for assessments. The goals of the REMS were 1) To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and 2) To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications. The REMS for Mifeprex incorporated the restrictions under which the drug was originally approved.

Since 2011, the Applicant has submitted two REMS assessment reports. The Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

FDA held a pre-NDA meeting with the Applicant on January 29, 2015, to discuss proposed labeling and REMS changes to be submitted in this efficacy supplement. These changes were submitted with the efficacy supplement.

The Applicant submitted published literature and supportive information to support changes to the dose, dosing regimen, gestational age, revisions to labeling, modifications to the REMS document, and to address PREA requirements. The Agency accepts the use of peer reviewed literature as primary data for an application under the framework of a 505(b)(2) application.

3. CMC

No new CMC information was submitted with this efficacy supplement. The CMC team determined no additional review or inspections were required. The CMC team completed a review of the labeling and found the CMC sections of labeling (sections 3, 11 and 16) acceptable (See review dated March 29, 2016). The CMC review team recommends approval of the efficacy supplement; refer also to the CMC review of the separate supplement proposing a single tablet blister pack for Mifeprex, dated January 11, 2016. There are no outstanding CMC issues or postmarketing commitments or requirements.

***Comment**: On March 10, 2016, a separate CMC supplement was approved that allowed the packaging of individual 200 mg tablets of mifepristone; previously packaging consisted of three 200 mg tablets per blister pack (a total of 600 mg Mifeprex as administered under the originally approved dosing regimen).*

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in this supplement. The Pharmacology/Toxicology team revised labeling to conform to the Pregnancy and Lactation Labeling Rule. There are no outstanding nonclinical issues. The Pharmacology/Toxicology review team recommends approval of the efficacy supplement; refer to the Pharmacology/Toxicology review dated March 4, 2016.

5. Clinical Pharmacology

The Applicant did not conduct any new clinical pharmacology studies pertaining to the proposed (b) (4) regimen, but provided information on pharmacokinetics (PK) of misoprostol following various routes of administration. The PK of the 200 mg Mifeprex tablet has not been characterized in women, but data are available in men and were submitted in the original NDA. The Clinical Pharmacology review team determined that the PK data were appropriate for inclusion in labeling. Review of the labeling pertinent to the Clinical Pharmacology sections is complete and labeling relevant to pharmacokinetics and pharmacodynamics is acceptable. There are no outstanding Clinical Pharmacology issues or postmarketing commitments or requirements. The clinical pharmacology review team recommends approval of the efficacy supplement; refer to the Clinical Pharmacology review dated March 29, 2016.

6. Clinical Microbiology

Not applicable.

7. Efficacy/Statistics

The Applicant submitted published literature as the primary evidence to support the efficacy (and safety) of the proposed dosing regimen (refer to the Clinical Review dated March 29, 2016, Section 9.5 for a list of submitted references). Most published articles submitted by the Applicant and reviewed by the clinical review team reported the primary efficacy endpoint as complete termination of pregnancy without further medical or surgical intervention; the Division considers this to be a clinically relevant endpoint.

The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent. The clinical review team concluded that the published literature was adequate as the primary information source to support the changes proposed in the efficacy supplement. During the course of the review, the team also requested and received more detailed information from select publications from their authors via communication with the Applicant.

Although there were slight demographic differences among the published studies from the database, these differences were not expected to alter the efficacy or safety of Mifeprex. Therefore, for the majority of the proposed efficacy changes, the clinical team assessed efficacy information from a subset of publications that evaluated a given proposed change. An independent statistical review was not needed for this review of published literature.

The clinical review team identified several major proposed clinical changes in the efficacy supplement. As these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes. These major changes as considered by the clinical team included:

1. A proposed dosing regimen consisting of mifepristone 200 mg orally followed by the buccal administration of 800 mcg misoprostol including:
    a. Use of a revised interval between mifepristone and misoprostol from 48 hours to 24-48 hours
    b. Allowing home administration of misoprostol
    c. Use of an additional dose of misoprostol
2. Support for extending the gestation age through 70 days
3. Flexibility in follow-up visit: follow-up is needed in the range of 7-14 days after Mifeprex administration; the specific nature and exact timing of the follow-up to be agreed upon by the healthcare provider and patient.
4. Change in who can provide Mifeprex from physician to healthcare provider who prescribes

The following section summarizes the clinical review team's evaluations that supported the above proposed changes:

1. *Support for the proposed dose and dosing regimen of 200 mg of Mifeprex orally and 800 mcg of misoprostol buccally 24-48 hours after Mifeprex administration:* The clinical review team reviewed the submission and identified studies and review articles that evaluated over 35,000 women who were treated with efficacy in the 91-98% range. For additional details on the efficacy from these studies, please refer to Section 6 of the Clinical Review.

2. *Support for extending the gestational age to 70 days:*
   The Applicant submitted a number of published articles and systematic reviews that supported the proposed dose and dosing regimen. Four studies and one systematic review evaluated the exact proposed dosing regimen through 70 days gestation. These include three prospective observational studies (Winikoff et al 2012[1], Boersma et al[2] , Sanhueza Smith et al[3]) and one randomized controlled trial (RCT) (Olavarrieta et al[4]) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin[5] covered 20 studies including over 30,000 women; all but one of the studies used the proposed regimen in gestations through 70 days (the remaining study used 400 mcg of buccal misoprostol). For those publications that provided overall success rates, these were in the range of 97-98%. Other relevant publications include the systematic review by Raymond[6] of 87 studies, which covered a variety of misoprostol doses and routes of administration used with 200 mg of mifepristone. Assessing the efficacy by misoprostol dose, the paper noted that doses ≥ 800 mcg had a success rate of 96.8%, with an ongoing pregnancy rate of 0.7%.

[1] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6
[2] Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011; 16: 61-6
[3] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015; 22: 75-82
[4] Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousieguez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ 2015; 93: 249-258
[5] Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015; 126(1): 12-21
[6] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

The original dosing regimen specifies taking misoprostol 2 days after Mifeprex. This efficacy supplement proposes a more flexible time frame of 24 to 48 hours between Mifeprex and misoprostol administration. Data from a review article by Wedisinghe et al[7] evaluated different time intervals using administration of misoprostol after Mifeprex. A meta-analysis of all five studies found a non-significant odds ratio for failure for shorter vs. longer dosing intervals, but a trend for lower success if a dosing interval < 8 hours is used. Chen & Creinin's systematic review[8] of 20 studies including over 33,000 women, all but one using the proposed regimen, compared the success of dosing intervals of 24 hours with intervals ranging from 24-48 hours. The success rate in six studies that used a 24-hour interval through 63 days gestation was 94.2%, compared to the rate of 96.8% in 14 studies that used a 24-48 hour interval, and this difference was statistically significant. The clinical team concluded that the efficacy of the revised dosing regimen was not compromised by revising the dosing interval to 24-48 hours. In addition, they noted that the overall rate of ongoing pregnancies did not differ significantly by dosing interval.

3. *Administration of misoprostol after Mifeprex administration at home:* Currently, the dosing regimen specifies that misoprostol is taken in the clinic setting following Mifeprex administration. No specific publication evaluated treatment outcomes with use of misoprostol at home compared to in-clinic dosing. However, one large literature review (Raymond et al[9]) evaluated a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration and dosing intervals used in gestations through 63 days. Roughly half of the studies included in this review did not require women to take misoprostol in-clinic. Rates of treatment failure and of ongoing pregnancy were very similar regardless of whether misoprostol was taken in-clinic or at another location. The clinical review team concluded that the review provided sufficient data to support labeling that misoprostol does not need to be restricted to in-clinic administration.

4. *Use of a repeat misoprostol dose, if necessary:* The Applicant submitted several published studies that supported use of a repeat misoprostol dose, when complete uterine expulsion did not occur after the initial misoprostol dose following Mifeprex. In clinical practice, the usual treatment for incomplete expulsion (retained products of conception) may include either a repeat dose of misoprostol, expectant management or a surgical procedure (suction aspiration or a dilation and curettage). Studies that specifically report the success rate of a repeat dose of misoprostol are:

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[7] Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. Contraception 2010; 81(4): 269-74. doi: 10.1016/ j.contraception.2009.09.007. Epub Oct 29, 2009

[8] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859

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

- Winikoff et al[10] – studied the proposed regimen through 70 days gestation; of the few women who received a second dose for an incomplete abortion at follow-up, the success rate was 91% at 57-63 days and 67% at 64-70 days.
- Chen and Creinin [11] – a systematic review of 20 studies, all but one of which used the proposed regimen up through 70 days; success of a second dose ranged from 91-100%
- Boersma et al[12] – included pregnancies through 70 days treated with the proposed regimen; five of 330 women took a second dose due to absence of bleeding 48 hours after first dose; the success rate was 80%
- Louie et al[13] – studied the proposed regimen to 63 days; in 16 women (of 863) who took a second dose of misoprostol, the success rate was 100%
- Chong et al[14] – compared the proposed regimen to a lower dose of misoprostol; the success of a second dose of misoprostol was 92% overall, but the number of women in each dose arm getting a second dose was not specified.
- Winikoff et al[15] – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%.

Using the information from the above studies and other supportive data, the clinical team concluded that the available data support the efficacy of a repeat dose of misoprostol if complete expulsion has not occurred. The relatively high complete pregnancy termination rates indicate that this option is likely to reduce the need for a surgical intervention.

5. *Requirements regarding follow-up care:* Current labeling states that women will return to the clinic 14 days after Mifeprex administration for follow-up. This provision was based on the follow up regimen in the U.S. phase 3 trial that supported the initial approval in 2000. Although the Applicant submitted several studies that evaluated flexibility in the time of follow-up, the key publication identified by the review team that addressed this issue was a 2013 article by

[10] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6
[11] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859
[12]Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011; 16: 61-6
[13] Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. Eur J Contracept Reprod Health Care 2014; 19(6): 457-464
[14] Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. Contraception 2012; 86: 251-256
[15] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008; 112(6): 1303-1310

Raymond[16]. The impact of the timing of follow-up was assessed in Raymond's systematic review of studies using various treatment regimens. While some have posited that earlier follow-up may result in a higher rate of surgical intervention (for women who would have had complete expulsion had they been given a bit more time), Raymond's analyses found no difference in failure rates for women followed less than one week after mifepristone as compared to a week or more after mifepristone. As follow-up was anticipated to not alter the efficacy of the proposing dosing regimen, this change is also discussed below in Section 7.

6. *Allowing qualified healthcare providers to use Mifeprex.*

   The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies included a study by Warriner et al[17] that showed efficacy of 97.4% with nurses versus 96.3% by physicians.

Conclusions: I concur with the clinical review team's assessments and conclusions and these conclusions will be reflected in labeling. The data and information reviewed constitute substantial evidence of efficacy to support the proposed dosing regimen for Mifeprex for pregnancy termination through 70 days gestation. Other proposed changes to the Mifeprex labeling, including the time interval between Mifeprex and misoprostol dosing, and use of a repeat dose, were also adequately supported by evidence. Finally, I concur with the clinical review team that the information from the published literature also supported efficacious use of Mifeprex by non-physician providers.

Comment: Discussion was held as to whether the original dosing regimen approved in 2000 (i.e., Mifeprex 600 mg and misoprostol 400 mcg up to 49 days gestation) should remain in labeling. (b) (4) the clinical review team and I concur with their (b) (4) request to remove the current regimen from the labeling. Removal of the original dosing regimen simplifies labeling, and avoids any confusion regarding instructions. Therefore, the revised labeling, and REMS materials accompanying the approval of this efficacy supplement, will include only the proposed dosing regimen and instructions. It should be noted that there are no safety or efficacy concerns about the originally approved dosing regimen that led to removing it from the labeling.

[16]Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.

[17] Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-61.

8. Safety

The safety of the proposed dosing regimen for Mifeprex was supported by the evidence from submitted published literature and postmarketing experience. The focus of the safety analysis was on published studies that evaluated the proposed dosing regimen (Mifeprex 200 mg followed by 800 mcg misoprostol buccally 24-48 hours later), with comparison to the known safety profile of the currently approved dosing regimen.

Exposure: Per the Applicant's submission, the clinical review concluded that there have been approximately 2.5 million uses of Mifeprex by U.S. women since the drug's approval in 2000. The clinical review team estimated that exposure to the proposed dosing regimen for their safety analysis was based on approximately 30,000 patients (refer to Table 11 for a list of references used to evaluate safety). Such exposure volume is sufficient to characterize the safety profile of the proposed dosing regimen and other proposed changes in this efficacy supplement.

Deaths: Deaths with medical abortion rarely occur and causality can be difficult to determine. Most of the publications did not specifically report any deaths with medical abortion with Mifeprex. Among the seven U.S. studies submitted to support the safety profile of Mifeprex and misoprostol, only one (Grossman, et al[18]) explicitly addressed deaths and noted that there were no deaths among 578 subjects evaluated in the study. Only one observational study (Goldstone, et al[19]) from Australia contained a report of a death after a mifepristone and misoprostol dosing regimen. In this retrospective review of 13,345 pregnancy terminations, the authors identified one death from sepsis. The article stated that the death was in an individual who failed to follow-up with her healthcare provider despite showing signs of illness. Based on this information, deaths in association with abortion are extremely rare.

Deaths reported from the postmarketing experience of Mifeprex are summarized below in the Postmarketing Experience section.

Nonfatal serious adverse events: The clinical review team identified key nonfatal serious adverse events (SAEs) associated with the proposed dosing regimen for Mifeprex. These SAEs include: hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. Section 7 of the clinical review dated March 29, 2016, provides a detailed discussion of reported rates of hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. The latter is not an adverse reaction because an ectopic pregnancy would exist prior to the Mifeprex regimen; it represents instead a failure to diagnose an ectopic pregnancy. Overall rates identified by the clinical review team from the published literature are as follows:

- Hospitalization: 0.04-0.6% in U.S. studies of over 14,000 women; 0-0.7% in international studies of over 1,200 women

[18]Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.
[19]Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. Med J Austral 2012; 197: 282-6.

- Serious infection/sepsis: 0-0.2% in U.S. and international studies of over 12,000 women
- Transfusion: 0.03-0.5% in U.S. studies of over 17,000 women; 0-0.1% in international studies of over 12,000 women

A study by Upadhyay et al[20] reported a 0.31% rate of major complications (including incomplete or failed abortion, hemorrhage, infection or uterine perforation that required hospitalization, surgery or transfusion) for medical abortions (dosing regimen unspecified) through 63 days; this was about double the rate reported for first trimester aspiration abortions and statistically significantly higher. However, these rates were driven by higher rates of incomplete/failed abortion; rates of hemorrhage (0.14%) and infection (0.23%) did not differ from those associated with aspirations.

Only one submitted study reported an ectopic pregnancy. This study (Winikoff et al[21]) reported one ectopic among 847 women (0.12%).

Comment: The proposed dosing regimen has been studied extensively in the literature using U.S. and global sites. Serious adverse events including deaths, hospitalization, serious infections, bleeding requiring transfusion and ectopic pregnancy are rarely reported. The rates of these serious adverse events are well below 1% and do not suggest a safety profile different from the original approved Mifeprex dosing regimen. Although there is less serious adverse event data on women who received Mifeprex and misoprostol between 64-70 days of gestation, the data from a U.S. study of 379 women (Winikoff et al)[22] in that gestational age is reassuring that the rates of these serious adverse events are not clinically different from that of other gestational age ranges.

In summary, based on the published literature, nonfatal serious adverse events occur with Mifeprex and misoprostol use with rates generally less than 1%. Increased gestational age (64-70 weeks) was not associated with an increased incidence of nonfatal SAEs. Other submission- specific safety issues that were evaluated including uterine rupture and angioedema/anaphylaxis are discussed in the Postmarketing Experience section below.

Loss to follow-up: The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc et al[23]) to 22% in the Grossman et al[24] study using telemedicine to deliver medical

[20]Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. Obstet Gynecol 2015;125(1):175-183.
[21]Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008;112(6):1303-1310.
[22]Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012;120:1070-6.
[23] Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. Obstet Gynecol 2014;123:88-95.
[24] Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.

abortion services.

Comment: Based on these data reviewed by the clinical review team, there is no literature that suggests that follow-up modality alters safety. Therefore, labeling will not be directive regarding follow-up; that will be a decision left to the patient and provider.

Common adverse events: The clinical review team evaluated common adverse reaction data and compared U.S. and global study locations. The comparison revealed that there were differences in the frequency of common adverse reactions, with the reporting rates considerably higher among the U.S. studies. There is no reason to anticipate regional differences in the safety profile for the same treatment regimen, so these differences likely reflect lower ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data in labeling would not be appropriate, as it is unlikely to be informative to the U.S. population of users. The data to be reported in labeling is outlined in Table 1 below:

Table 1: Common Adverse Events (≥ 15%) in U.S. Studies of the Proposed Dosing Regimen

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

Source: Data from Middleton[25], Winikoff[26] and Winikoff[27] as outlined in Table 2 of the CDTL review dated March 29, 2016.

One concerning adverse event is severe vaginal bleeding. Severe vaginal bleeding can result in interventions such as hospitalization and transfusion and may be associated with infection. The overall rate of bleeding across publications varied between 0.5% and 4.2%. Two publications (Sanhueza Smith et al[28] and Gatter et al[29]) evaluated clinically significant bleeding by gestational age. Although the publications reported slightly different rates, there was no trend of increased bleeding requiring intervention with Mifeprex and misoprostol use with increasing gestational age.

[25] Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005; 72: 328-32

[26] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6

[27] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008; 112(6): 1303-1310

[28] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015;22:75-82.

[29] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.

Comment: While not all of the studies reported common adverse events, those that reported did not have unexpected rates of common adverse events. These common adverse events are included in labeling in section 6.1 (Clinical Trial Experience) in the ADVERSE REACTIONS section.

Postmarketing experience – Spontaneous reports:

The safety profile for Mifeprex includes over 15 years of postmarketing safety data available on Mifeprex due to the reporting requirements under the REMS. The Year 3 REMS Assessment report was submitted by the Applicant in June, 2015. The (b) (6) (b) (6) provided a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. Findings include:

- No Clostridial septic deaths reported in the U.S. since 2009, and none worldwide since 2010.
- The postmarketing rates of hospitalization, severe infection, blood loss requiring transfusion and ectopic pregnancy reported from publications and remain stable and relatively low.

Submission-specific safety issues:

- Anaphylaxis/angioedema: The (b) (6) ((b) (6) identified a safety signal of anaphylaxis and angioedema with mifepristone administration. This signal was based on a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema. There were no additional cases of anaphylaxis or angioedema identified in the literature.

  Comment: (b) (6) and the clinical review team recommended that anaphylaxis and angioedema be described in the Contraindications and Adverse Reactions sections of labeling. These labeling sections were discussed with the Applicant and labeling was revised for those sections to describe these serious adverse events.

- Uterine rupture: As discussed in the clinical review, the potential risk of uterine rupture was considered because the current labeling for misoprostol includes a Boxed Warning against the use of misoprostol for gestations more than 8 weeks due to the risk of uterine rupture. Although misoprostol is used alone for various obstetric indications, including induction of labor at term, it was important to consider whether labeling about this potential risk is warranted for Mifeprex. Both the clinical reviewer and the (b) (6) ((b) (6) reviewed the literature and (b) (6) searched FAERS for adverse event reports.

Published literature reported three case reports[30,31,32] of uterine rupture with mifepristone/misoprostol treatment in the first trimester. Of these three reports, two patients had a risk factor for uterine rupture (prior uterine surgery). The third case was in a patient who received more than two doses of misoprostol. After consideration, the clinical review team decided that labeling should include information about this event. The FAERS search did not identify any reports of uterine rupture with use of mifepristone alone. Of 80 reports, 77 cited use of misoprostol alone, and three of mifepristone and misoprostol. Only two reports of uterine rupture in the first trimester were identified, both using misoprostol alone; one entailed an unspecified dose and route of misoprostol at 5 weeks gestation, and one involved vaginal administration of 800 mcg misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar.

Based on the available safety reports of uterine rupture, the review team from (b) (6) and clinical review team concluded that these data demonstrated that uterine rupture with Mifeprex and misoprostol in the first ten weeks (70 days) of gestation is exceedingly uncommon, and occurs most often in the face of a risk factor (previous uterine surgery).

Comment: I agree with the clinical review team and the (b) (6) team that the risk of uterine rupture with first trimester use of mifepristone and misoprostol appears to be extremely rare, and most often associated with a prior uterine scar, a known risk factor for uterine rupture. Labeling of these reports is included in section 2.3 of the DOSAGE AND ADMINISTRATION and section 6.2 of the ADVERSE REACTIONS of labeling to provide additional information to healthcare providers, but no restriction of use is needed based upon this extremely rare adverse reaction.

The clinical review team also evaluated the safety for each of the following major changes proposed in this efficacy supplement:

1. Changing the dosing interval between Mifeprex and misoprostol from 48 hours to 24-48 hours
2. Home administration of misoprostol
3. Use of a repeat dose of misoprostol
4. Change in the follow-up timeframe and method of follow-up
5. Allowing providers other than physicians to provide Mifeprex

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[30] Khan S et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. Journal of Obstet Gynaecol 2007; 27: 869-870

[31] Bika O, Huned D, Jha S, Selby K Uterine rupture following termination of pregnancy in a scarred uterus J Obstet Gynaecol 2014; 34(2): 198-9. doi: 10.3109/01443615.2013.841132

[32] Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. BJOG 2008;15:575-77

To evaluate each of these changes, the reviewers evaluated the adverse event information regarding:

- *Changing the timing interval between Mifeprex and misoprostol and change in the gestational age to 70 days:* Support for the 24-48 hour interval and use up through 70 days was primarily based on a large systematic review by Shaw et al[33]. This review evaluated studies looking at different follow-up modalities and demonstrated that there are a variety of acceptable alternatives to in-clinic follow-up that can identify cases in which there is need for additional intervention. In addition, the systematic review did not identify any significant difference in adverse events with different time intervals. Based on these findings, labeling will not be directive regarding specific details of how follow-up should be performed; this will be a decision between the patient and her healthcare provider.

- *Home administration of misoprostol:* The Applicant supplied several published studies that supported this change including Gatter et al[34] and Ireland et al[35]. These studies reported on large numbers of women in the U.S. who took misoprostol at home. The authors showed that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the studies of clinic administration of misoprostol that supported the initial approval in 2000. Given that information is available on approximately 45,000 women from the published literature, half of which incorporated home use of misoprostol, there is no clinical reason to restrict the location in which misoprostol may be taken. Given the fact that the onset of cramping and bleeding occurs rapidly (i.e., generally within 2 hours) after misoprostol dosing, allowing dosing at home increases the chance that the woman will be in an appropriate and safe location when the process begins.

- *Use of a repeat dose of misoprostol:* Safety reporting from studies that evaluated a repeat dose of misoprostol did not specifically assess the subset of women who received a second dose, but no unexpected findings were identified. One randomized controlled trial (Coyaji et al[36]) conducted in 300 women seeking medical abortion in India looked at a single misoprostol dose as compared to two misoprostol doses. Although there was no difference in the complete pregnancy termination rate in women who received a second misoprostol dose compared to those who did not, the repeat misoprostol dose reduced the need for surgical intervention. This study was reassuring in that there was no significant difference in the adverse events observed—similar percentages of women experienced

[33] Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. Obstet Gynecol 2013;121(6):1335-1347.
[34] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[35]Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. Obstet Gynecol 2015;126:22-8.
[36] Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? BJOG 2007;114:271-278.

cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). A supportive systematic review by Gallo et al[37] also provided safety information on subjects who received repeat misoprostol. In this review, the only side effects discussed in the trials were diarrhea, which was more common on those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported <1%. Based on these findings, labeling will be changed because the misoprostol dose does not need to be restricted to in clinic administration to assure safe pregnancy termination using the proposed dosing regimen. Given the onset of bleeding and cramping after misoprostol, allowing home administration increases the likelihood that a woman will be in an appropriate and safe location when the pregnancy termination process begins.

- *Change in the follow-up timeframe and method of follow-up:* The Applicant submitted several articles that described different methodologies in follow-up including phone calls and standardized instructions. The clinical reviewers evaluated a study in Scotland by Cameron et al[38] that evaluated self-assessment as compared to standard follow-up methodologies (clinic visit or phone call). Most of the women chose self-assessment over an in-clinic visit or phone call, and there were no significant differences in adverse outcomes between women who underwent self-assessment of health compared to those who had a clinic visit or phone call. Among women with an ongoing pregnancy after Mifeprex and misoprostol, the majority self-identified and presented within two-weeks for care. Based on this information and the other data from the Raymond systematic article[39] that did not identify a difference in failure rate for earlier (less than one week) as compared to one week or greater of follow-up, sufficient support was provided to use a broadened window of 7 to 14 days for follow-up. This revised follow-up time frame will be included in labeling.

- *Allowing providers other than physicians to provide Mifeprex*: The current Prescriber's Agreement in the REMS specifies that "…Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications…" In addition, current labeling states that Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. However, labeling states that other healthcare providers, acting under the supervision of a qualified physician, may also provide Mifeprex to patients. Several published studies submitted by the Applicant indicate that health care providers such as nurse practitioners, nurse midwives, and physician assistants are

[37] Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. Contraception 2006;74:36-41.
[38] Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? Contraception 2015;91:6-11.
[39] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

currently providing abortion services. One of these studies (Kopp Kallner et al[40]) was a randomized controlled trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. Success rates were ≥ 96% regardless of gestational age. The nurse midwife group had few complications, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, p=0.14). No serious complications were reported and no blood transfusions were administered in the study. Based on this and other supportive studies, the information supports the efficacy and safety of allowing healthcare providers other than physicians can effectively and safely provide abortion services, provided that they meet the requirements for certification described in the REMS. The clinical team also felt that the term "healthcare provider who prescribes" would be the appropriate terminology as prescribing ability is a critical factor in dispensing Mifeprex.

The clinical review team concluded that the evidence demonstrated acceptable safety for each of the above proposed changes, and I concur with their conclusion. The proposed dosing regimen has a similar safety profile as the original regimen approved in 2000. Adverse outcomes of interest, such as deaths, serious infection, transfusions, ectopic pregnancies and uterine rupture, remain rare, and are not necessarily attributable to Mifeprex use. Overall, the rate of deaths and nonfatal serious adverse events are acceptably low, and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen No association between adverse outcomes and increasing gestational age was identified. Finally, the available information supports the safety of the other proposed changes, including increasing the flexibility of the time interval between Mifeprex and misoprostol, at home use of misoprostol, use of a repeat dose of misoprostol, change in the follow-up timeframe and allowing health care providers other than physicians to prescribe and dispense Mifeprex were acceptable.

9. Advisory Committee Meeting

Mifeprex is not a new molecular entity requiring discussion before an advisory committee. In addition, an advisory committee was not necessary as the application did not raise complex scientific or other issues that would warrant holding an AC before approval.

10. Pediatrics

This efficacy supplement triggered requirements under the Pediatric Research Equity Act (PREA). The Agency granted a partial PREA waiver for pre-menarcheal females ages birth to 12 years because it would be impossible to conduct studies in this pediatric population, as pregnancy does not exist in premenarcheal females.

[40] Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. Human Reprod 2010;25(5):1153-1157.

The Applicant fulfilled the remaining PREA requirement in postmenarcheal females by submitting published studies of Mifeprex for pregnancy termination in postmenarcheal females less than 17 years old. Efficacy and safety information in these adolescents was based on a U.S. study in 322 postmenarcheal adolescents (Gatter et al[41]). Of the 322 adolescents, 106 of these adolescents were under 16; see Table 2 below:

Table 2: Age and Number of Adolescents Undergoing Medical Abortion (Gatter et al[42])

Age of Subject	Number of Subjects evaluated
11	1
12	1
13	2
14	20
15	82
16	216

Source: Refer to Table 17 of the Medical Officer's review dated March 29, 2016

The Gatter et al[43] study reported that postmenarchal females less than 18 years old had a 98.7% pregnancy termination rate as compared to females aged 18-24, who had a rate of 98.1%. This article reported that loss to follow-up was slightly higher in those less than 18 years old, however, age did not adversely impact efficacy outcomes.

One issue was whether adolescents would comply with at home use of misoprostol. The Gatter[44] et al study incorporated at home use of misoprostol into the Mifeprex dose regimen given to all females, including postmenarchal females less than 18 years old. The overall efficacy in adolescents was similar to that of all older women. This information supports at home administration of misoprostol in postmenarchal females under 17.

Two other published studies provided additional efficacy on Mifeprex use by adolescents for pregnancy termination:

- Phelps et al[45] evaluated data from 28 adolescents aged 14 to 17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. In this study, 100% of subjects had a complete pregnancy termination, with five not requiring misoprostol.

[41]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[42] Ibid.
[43]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[44]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[45]Phelps RH, et al. Mifepristone abortion in minors. Contraception 2001;64:339-343.

- Niinimaki et al[46] used data from a Finnish Registry from 2000-2006. An analysis of efficacy between adolescents under age 18 compared to the women ≥ age 18 indicated that the adolescent group had a lower rate of incomplete abortions as compared to adults. And efficacy outcomes in adolescents were similar to those of adult women.

The safety of Mifeprex in postmenarcheal adolescents was primarily supported by adverse event information from the Gatter et al[47] study. (b) (6), (b) (4) Supportive data from a Finnish registry (Niinimaki et al) from 3024 adolescent females under 18 years of age reported that, compared to adult women, the risks of hemorrhage (adjusted odds ratio 0.87 [95% confidence interval: 0.77 to 0.99]), incomplete abortion (0.69, [95% confidence interval: 0.59 to 0.82]), and surgical evacuation (0.78, [95% confidence interval: 0.67 to 0.90]) were lower in the adolescent cohort. In the Finnish registry study, a majority of adolescents and adults received both Mifeprex and misoprostol. Safety findings from the Gatter et al and Niinimaki et al studies are reassuring and indicate that the safety profile of Mifeprex is similar between postmenarcheal adolescents and adult women.

Additional details from this article and other published data on Mifeprex use in adolescents (females under 17) are described in the clinical review (Refer to the Medical Officer's review dated March 29, 2016).

(b) (6) concurred that the efficacy and safety data in postmenarcheal adolescents less than 17 years old was sufficient to support the use of Mifeprex in this pediatric population and to fulfill the PREA pediatric study requirement. The revised Mifeprex labeling will state that that efficacy and safety are similar to adult women in the Pediatric Use section (8.4).

11. Other Relevant Regulatory Issues

(b) (6)

reviewed the Medication Guide in conjunction with the (b) (6) ((b) (6) Both (b) (6) and (b) (6) found the Medication Guide to be acceptable with recommended changes (See review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in

[46]Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.
[47]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[48]Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

the Medication Guide and incorporated appropriate changes into the final agreed upon Medication Guide.

[redacted] reviewed the Prescribing Information (PI) in addition to the joint review with [redacted] of the Medication Guide in conjunction with [redacted] After review, [redacted] provided recommended changes (See [redacted] review dated March 29, 2016). The Division considered all of the recommendations from [redacted] in revising and updating the text in the PI and incorporated appropriate changes into the final label.

[redacted] in the [redacted]) reviewed the proposed modifications to the REMS. The [redacted] review reflected agreement with the Applicant's proposed REMS changes which include:

- Removal of the term "under Federal law" from the Prescriber's Agreement.
- Replacement of the word "physician" with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex. [redacted] believes that the Applicant's proposed terminology of "[redacted] is too broad and that a more appropriate description is "healthcare provider who prescribes," which limits acceptable healthcare providers to those who are licensed in their state to prescribe medications.
- Removal of the Medication Guide from the REMS. The Medication Guide remains an important education tool for patients. It will still be dispensed to each patient in accordance with 21 CFR part 208. As described in the Medication Guide Guidance, a Medication Guide is not necessary to ensure that the benefits outweigh the risks of Mifeprex
- Modification of Element to Assure Safe Use (ETASU) A, the Prescriber's Agreement. [redacted] recommends changing the name of the document to the Prescriber's Agreement Form to be consistent with other REMS programs. References to "physician" should be changed to "healthcare provider who prescribes."
- [redacted] recommends removing the Patient Agreement from the REMS for a number of reasons:
  1. The established safety profile over 15 years of experience with Mifeprex is well-characterized, stable, and known serious risks occur rarely
  2. The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208
  3. The Prescriber's Agreement Form will continue to require providers to explain the treatment, its effects and risks associated with Mifeprex and to answer any questions that a patient may have
  4. Established clinical practice provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment. FDA has removed REMS

requirements in other programs based on the integration of the REMS safe use condition into clinical practice.

Other revisions to the REMS document will be made for consistency with changes described above and to reflect current FDA thinking and practice regarding format, language and flow in REMS documents. These changes include modification of the Mifeprex REMS goal, changes in requirements to certify prescribers (removal of the requirement to obtain a Patient Agreement) and other minor edits.

In summary, the overall (b) (6) recommendation for the REMS modification for this efficacy supplement was approval (Refer to (b) (6) review dated March 29, 2016).

12. Labeling

Carton and container labeling was reviewed by the (b) (6) ((b) (6) the (b) (6) ((b) (6) and the (b) (6) ((b) (6) (b) (6) Their comments were conveyed to the Applicant as appropriate.

The label was submitted in the format prescribed by the PLR. Although the supplement was submitted prior to when it would otherwise have been required to comply with the PLLR requirements, the review team believed it would be of value to harmonize with this labeling standard to the extent possible.

Specific issues discussed during labeling negotiations included the selection of studies for inclusion in Section 6.1 (Clinical Trial Experience in the ADVERSE REACTIONS section) and 14 (CLINICAL STUDIES section). Only studies that evaluated the specific proposed regimen were included in these sections. For the Adverse Reactions section, examination of the common adverse reaction data by U.S. compared to non-U.S. study location revealed that there were large differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the U.S. studies. This may reflect differences in ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data would not be appropriate, as it is unlikely to be informative to the U.S. population of users. In the case of serious adverse reactions, the reported frequency was quite similar regardless of study location; for this reason, serious adverse reaction information from global studies is reported. Agreement on labeling was reached on March 29, 2016.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

Postmarketing Requirements/Postmarketing Commitments: None.

Risk Evaluation and Mitigation Strategies (REMS): The Applicant proposed a REMS modification for the Mifeprex REMS program with the submission of this efficacy supplement. The review teams from the (b) (6) evaluated the current Mifeprex REMS program and the proposed REMS modifications to determine whether each Mifeprex REMS element remains necessary to ensure that the benefits of Mifeprex outweigh the risks. Factors that impacted the decision included findings from two REMS assessments (the more recent REMS assessment review was completed in October 2015), an unchanged safety profile, and published literature that documented adequate safeguards in clinical practice with the use of Mifeprex in a regimen with misoprostol.

The teams determined that the following REMS modifications were warranted:

1. Revisions to the Prescriber Agreement Form to reflect the new dosing regimen and to reflect current REMS formatting and language standards
2. Removal of the Medication Guide as a REMS element, as distribution of the Medication Guide is required under 21 CFR 208
3. Removal of the Patient Agreement as a Documentation of Safe Use Condition (ETASU D)
4. Updating of the REMS goals to reflect the above 3 changes.
5. Removal of the phrase "Under Federal law" from the Prescriber's Agreement
6. Replacing the term "licensed physician" with "healthcare provider who prescribes"

The above modifications to the Mifeprex REMS program were discussed with the (b) (6) (b) (6) on January 15, 2016, as per (b) (6) .

The (b) (6) concurred with conforming changes to the Prescriber's Agreement to reflect the new dosing regimen, and with removal of the Medication Guide from the REMS. The Medication Guide would remain a part of labeling to inform patients about the risks associated with Mifeprex use. The (b) (6) also concurred with revisions to the REMS goals to reflect these changes.

The (b) (6) concurred with the removal of the term "under Federal law". A rationale for the original inclusion of the phrase "Under Federal law" cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and it was decided that the phrase be removed from the Prescriber's Agreement.

The (b) (6) concurred with use of the term "healthcare providers who prescribe." To support a change in the REMS that would allow qualified healthcare providers other than physicians to prescribe Mifeprex through the Mifeprex REMS program, the Applicant provided information from over 3,200 women in randomized controlled trials and 596 women in prospective cohort studies comparing medical abortion care by physicians versus other providers (nurses or nurse midwives). These studies were conducted in a variety of settings (international, urban, rural, and low-resource). No differences in serious adverse events, ongoing pregnancy or incomplete abortion were identified between the groups. Given that providers other than physicians are providing family planning and abortion care under supervision and that the approved labeling and REMS program stipulate that prescribers must be able to refer patients for additional care, including surgical management, allowing these prescribers to participate in the Mifeprex REMS program is acceptable.

The (b) (6) also concurred with the teams' recommendation to remove the Patient Agreement (ETASU D) from the REMS although some (b) (6) members commented that additional support for the review team's rationale for this modification was needed. The review team's rationale for this change was:

APPEARS THIS WAY ON ORIGINAL

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and Informed Consent, and, more specifically with Mifeprex, includes counseling on all options for termination of pregnancy, access to pain management and emergency services if needed.
- Medical abortion with Mifeprex is provided by a well-established group of organizations and their associated providers who are knowledgeable in this area of women's health. Their documents and guidelines cover all the safety information that also appears in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the direct supervision of a certified prescriber.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

The Mifeprex REMS program will have a modified ETASU REMS that will continue to ensure that Mifeprex can only be prescribed by certified prescribers and be dispensed to patients in certain healthcare settings, specifically, clinics, medical offices and hospitals. The Medication Guide will continue to be distributed to patients required under 21 CFR part 208. As required for all ETASU REMS, ongoing assessments of the Mifeprex REMS program will continue to ensure that the modified Mifeprex REMS program is meeting its goals.

13. Decision/Action/Risk Benefit Assessment

Decision:

All regulatory and scientific requirements have been adequately addressed in this efficacy supplement. Review teams involved in this supplement have recommended approval of the supplement from their disciplines' perspective. The submitted efficacy and safety information supported approval of the proposed dosing regimen through 70 days gestation, and other changes discussed in this summary memo. This supplement will receive an Approval action.

Benefit Risk Assessment:

This efficacy supplement provided substantial evidence of efficacy for the proposed dosing regimen through 70 days gestation. The efficacy findings were similar to those that led to the approval of the original dosing regimen in 2000. In addition, the submitted published literature supported other changes sought in this efficacy supplement that will

be reflected in labeling: 1) a more flexible time interval of 24 to 48 hours between Mifeprex and misoprostol administration, 2) the option of at home administration of misoprostol, 3) the option of repeat misoprostol dosing, if clinically indicated, 4) flexibility in the follow–up time frame of 7 to 14 days, and 5) permitting qualified healthcare providers other than physicians to prescribe Mifeprex.

The safety findings of the proposed dosing regimen were acceptable and were similar to those seen with the original dosing regimen approved in 2000.

After review of the REMS modifications proposed by the Sponsor, I concur with the clinical team and (b) (6) recommendations that:

1. The Medication Guide can be removed from the Mifeprex REMS program. The Medication Guide requirements under 21 CFR part 208 require the Medication Guide to be distributed to patients. Mifeprex will only be dispensed by a healthcare professional who will be knowledgeable and able to provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or follow-up that may be required as appropriate, and who will answer any questions the patient may have. In that setting, the Medication Guide will already be a required available tool for counseling. Therefore, given the existing requirements under 21 CFR part 208, I concur that there is no reason for the Medication Guide to specifically be a part of the REMS.

2. The Prescriber Agreement Form (ETASU A) as revised reflects current FDA format and content to conform to current REMS programs and reflect the labeling changes that will be approved in this supplement. I concur that the changes are acceptable.

3. Revision of the Mifeprex REMS goals (ETASU C) will adequately mitigate the risk of serious complications by requiring certification of healthcare providers who prescribe and ensuring the Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber.

4. Removal of the Patient Agreement Form (ETASU D): I concur with the clinical review team that the Patient Agreement Form, which requires a patient's signature, does not add to safe use conditions for the patient for this REMS and is a burden for patients. It is standard of care for patients undergoing pregnancy termination to undergo extensive counseling and informed consent. The Patient Agreement Form contains duplicative information already provided by each healthcare provider or clinic. I believe that it is much more critical for the healthcare provider who orders or prescribes Mifeprex to provide and discuss informed consent derived from their own practice so that care can be individualized for the patient.

I support that the Mifeprex REMS with ETASUs A and C remain in place to support conditions critical to the use of the drug. Therefore, the implementation system and timetable for assessments should continue.

I also agree with the clinical review team that the reporting requirements should only be required for deaths. It is important that the Agency be informed of any deaths with Mifeprex to monitor new safety signals or trends. However, after 15 years of reporting serious adverse events, the safety profile for Mifeprex is essentially unchanged. Therefore, I agree that reporting of labeled serious adverse events other than deaths can be collected in the periodic safety update reports and annual reports to the Agency.

In summary, I believe that the benefit-risk profile for Mifeprex continues to be favorable and with the agreed-to labeling changes and REMS modifications, the Mifeprex REMS program will continue to assure safe use. Therefore, I support approval of this efficacy supplement and REMS modifications.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked [redacted] (b) (6) and the [redacted] (b) (6) to continue to include a Patient Agreement Form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through the [redacted] (b) (6) (6) Therefore, the Patient Agreement Form will be retained and other changes will be made in the REMS to reflect that it is being retained.

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

/s/

(b) (6)

03/29/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

SUMMARY REVIEW

[redacted] and [redacted]

Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 091178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequences 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022 (sequences 24 and 92 respectively), December 9, 2022 (sequences 25 and 93 respectively) and December 16, 2022 (sequences 26 and 95 respectively). This supplement is on a 180-Day clock.
Targeted Action Date	December 19, 2022
[redacted] #	2022-1169
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	January 3, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS
Name of Sponsor	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

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EXECUTIVE SUMMARY

This is a review of the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178. The Sponsors submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, and amended their submissions on October 19, 2022 (Danco), October 20, 2022 (GBP), November 30, 2022 (both), December 9, 2022 (both) and December 16, 2022 (both).

The Mifepristone REMS Program was originally approved on April 11, 2019, to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021.[a] The Mifepristone REMS Program consists of elements to assure safe use (ETASU) A, C and D, an implementation system, and a timetable for submission of assessments of the REMS.

The Sponsors submitted the proposed modification to the REMS in response to the Agency's REMS Modification Notification letters dated December 16, 2021, which required removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") and the addition of certification of pharmacies that dispense the drug.

In addition, the following were addressed during the course of the review:

- revisions to the REMS goal to align with the updated REMS requirements.
- replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms*, *Patient Agreement Form*, and *Pharmacy Agreement Forms*).

The review team finds the proposed modification to the Mifepristone REMS Program last submitted on December 16, 2022, to be acceptable and recommends approval of the REMS modification. The proposed REMS modification includes changes to the REMS goal, additional REMS requirements for prescribers to incorporate dispensing from certified pharmacies and new REMS requirements for pharmacy certification.

The proposed goal of the modified REMS for mifepristone 200 mg is to mitigate the risk of serious complications associated with mifepristone by:

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

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

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

[a] The May 14, 2021 REMS modification approved the inclusion of gender neutral language in the Patient Agreement Form as well as corresponding minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

The timetable for submission of assessments of the REMS was modified to one year from the date of the approval of the modified REMS and annually thereafter. The assessment plan was revised to align with the changes to the REMS and capture additional metrics for drug utilization and REMS operations.

The modified REMS includes ETASU A, B and D, an implementation system, and a timetable for submission of assessments of the REMS. Mifepristone will no longer be required to be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement" for brevity) and will be able to be dispensed from certified pharmacies.

1. Introduction

This review evaluates the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Sponsors initially submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, in response to the Agency's REMS Modification Notification letters issued on December 16, 2021, to Danco and GBP, requiring the following modification to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

Per the Agency's December 16, 2021, REMS Modification Notification letters, the proposed REMS was required to include the following ETASU to mitigate the risk of serious complications associated with mifepristone, including at least the following:

- healthcare providers have particular experience or training, or are specially certified
- pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- the drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS was also required to include an implementation system and timetable for submission of assessments.

2. Background

2.1. Product Information and REMS Information

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed

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

the risk of serious complications associated with mifepristone when used for medical abortion.[c] Mifeprex was deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and the Mifeprex REMS was approved on June 8, 2011.

On March 29, 2016, FDA approved an efficacy supplement for Mifeprex, which included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol, as well as a modification of the gestational age up to which Mifeprex has been shown to be safe and effective and a modification to the process for follow-up after administration of the drug. FDA also approved modification to the Mifeprex REMS that reflected the changes approved in the efficacy supplement.[1-5] On April 11, 2019, FDA approved ANDA 091178 and the Mifepristone REMS Program.[6-7] The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 091178. The goal of the approved Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber (under ETASU C).
c) Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

The Mifepristone REMS Program was last modified and approved in 2021 to revise the *Patient Agreement Form* to include gender-neutral language; however, the goal of the Mifepristone REMS Program has not changed since the initial approval in 2019.

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and agree to follow the guidelines for use of mifepristone. Under ETASU C, in the Mifepristone REMS Program as approved prior to today's action, mifepristone was required to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The approved Mifepristone REMS Program includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public health emergency (PHE) regarding the in-person dispensing requirement in the Mifepristone REMS Program. Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020, to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[8]

[c] Mifepristone is also approved in approximately 80 other countries. https://gynuity.org/assets/resources/biblio_ref_lst_mife_en.pdf

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 04/11/2019: Approval of the Mifepristone REMS Program, a single, shared system REMS that includes NDA 020687 and ANDA 091178.
- 04/12/2021: The Agency issued a General Advice letter to both the NDA and ANDA Applicants, explaining that FDA intended to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.
- 05/07/2021: The Agency stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with section 505-1 of the FD&C Act.
- 12/16/2021: The Agency completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification.[9]
- 12/16/2021: REMS Modification Notification letters were sent to both Sponsors stating that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare system of complying with the REMS and ensure that the benefits of the drug outweigh the risks.
- 04/08/2022: Final written responses to a Type A meeting request were provided to Danco, the point of contact for the Mifepristone REMS Program. The questions pertained to the 12/16/2021 REMS Modification Notification letter requirements.
- 04/13/2022: The Sponsors requested an extension to 6/30/2022, to submit a proposed REMS modification in response to the Agency's 12/16/2021 REMS Modification Notification letters.
- 04/15/2022: The Agency granted the Sponsors' request for an extension to submit a proposed REMS modification and conveyed that the modification must be submitted no later than 06/30/2022.[10]
- 06/22/2022: Danco and GBP submitted a proposed REMS modification to their respective applications in response to the 12/16/2021 REMS Modification Notification letters.
- 07/22/2022: An Information Request was sent to the Sponsors requesting clarification of the proposed prescriber and dispenser requirements and additional rationale to support their proposal.
- 08/26/2022: Sponsors submitted responses to 07/22/2022 Information Request.
- 09/19/2022: Teleconference was held between Agency and Sponsors where the Agency communicated the REMS requirements that are necessary to support the addition of pharmacy

certification. The Agency proposed focusing on the pharmacy settings where a closed system[d] REMS could be implemented using the existing email and facsimile based system, (b) (4) , as the best strategy for an approvable modification by the goal date.

- 09/22/2022: An Information Request was sent to Sponsors requesting confirmation that the Sponsors agree with the pharmacy distribution approach outlined in the 09/19/2022 teleconference so that the Agency's feedback could be appropriately tailored.
- 09/23/2022: The Sponsors confirmed via email that they were willing to pursue (b) (4) , as discussed in the 09/19/2022 teleconference. The Sponsors also requested a teleconference to discuss the current modification (b) (4) .
- 09/27/2022: Comments from the 09/19/2022 teleconference sent to Sponsors with additional comments and requests regarding what will be necessary for pharmacy certification.
- 09/29/2022: An Information request was sent to the Sponsors asking for agenda items, questions, and a request to walk through their proposed system for pharmacy certification, including dispensing through mail-order or specialty pharmacies, at the 10/06/2022 scheduled teleconference.
- 10/04/2022: Sponsors emailed that they will focus the 10/06/2022 teleconference on the 09/27/2022 Agency comments and their mail order and specialty pharmacy distribution model.
- 10/06/2022: Teleconference was held between Agency and Sponsors where Sponsors outlined their proposal for pharmacy certification, including dispensing through mail order and specialty pharmacies, as well as their concerns with certain requirements and general timelines.
- 10/19/2022: Danco submitted a REMS amendment to their pending sNDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/20/2022: GBP submitted a REMS amendment to their pending sANDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/25/2022: Teleconference was held between Agency and Sponsors to discuss the *Patient Agreement Form* and timing related to shipping a mifepristone prescription from a certified pharmacy to the patient.
- 11/23/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document, submitted on 10/19/2022 (Danco) and 10/20/2022 (GBP).
- 11/30/2022: Danco and GBP submitted REMS amendments, which included the REMS Document, to their respective pending supplemental applications.
- 12/01/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document.
- 12/05/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document submitted on 11/30/2022 and discussed at the teleconference on 12/01/2022, and REMS materials submitted to their applications on 10/19/2022 and 10/20/2022.

[d] "Closed system" in this case refers to a system where prescribers, pharmacies, and distributors are certified or authorized in the REMS and the certification of the stakeholder must be verified prior to distribution or dispensing, as per the REMS.

- 12/07/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document and REMS materials the Agency sent to the Sponsors on 12/05/22.
- 12/08/2022: Danco and GBP submitted REMS amendments, including the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form, Patient Agreement Form* and REMS Supporting Document, to their respective pending applications.
- 12/09/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS assessment plan.
- 12/14/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form*, and REMS Supporting Document.
- 12/15/2022: Two teleconferences were held between Agency and Sponsors to discuss the proposed REMS Document and REMS materials the Agency sent to the Sponsors on 12/14/22.
- 12/16/2022: Sponsors submitted a REMS amendment to their respective applications.

3. Review of Proposed REMS Modification

(b) (6) has discussed the Sponsors' proposed modification with the review team, which includes members of the (b) (6) and the (b) (6) ; hereafter referred to as the review team. This review includes their input and concurrence with the analysis and proposed changes to the Mifepristone REMS Program.

3.1. REMS Goal

The Sponsors proposed modification to the goal for the Mifepristone REMS Program to add that mifepristone can also be dispensed from certified pharmacies on prescriptions issued by certified prescribers. The proposed REMS goal is:

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

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

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

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

Reviewer Comment: *We agree with the Sponsors' proposal.*

3.2. REMS Document

The proposed REMS Document is not in the format as outlined in the 2017 Draft Guidance for Industry, Format and Content of a REMS Document.[11]

Reviewer Comment: *To avoid the misperception that this REMS modification is making major changes to the REMS document that go beyond our December 16, 2021, determination that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification, CDER staff and management discussed whether to change the format of the REMS document to that described in the 2017 draft guidance.[11] After internal discussion, CDER staff and management aligned not to transition the REMS document at this time to the format described in the 2017 draft guidance.*

3.3. REMS Requirements

3.3.1. Addition and Removal of ETASU

The December 16, 2021, REMS Modification Notification letters specified that the ETASU must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure the benefits of the drug outweigh the risks by:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices and hospitals (i.e., the "in-person dispensing requirement"), and;
- Adding a requirement that pharmacies that dispense the drug be specially certified.

The Sponsors proposed changes to the REMS as reflected in the subsections below.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Prescriber Requirements

Consistent with the approved Mifepristone REMS Program prescribers must be specially certified. To become specially certified to prescribe mifepristone, healthcare providers who prescribe must review the Prescribing Information for mifepristone and complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet certain qualifications and will follow the guidelines for use of mifepristone. The guidelines for use include ensuring i) that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained; ii) that the healthcare provider (HCP) and the patient sign the *Patient Agreement Form*, iii) the patient receives a copy of the *Patient Agreement Form* and Medication Guide, iv) the *Patient Agreement Form* is placed in the patient's medical record; v) that any patient deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient. The language on the guidelines for use was revised from the Mifepristone REMS Program approved in 2021 to clarify that, if the certified prescriber supervises the dispensing of mifepristone, they must ensure the guidelines for use of mifepristone are followed by those under their supervision. This clarification reflects the ongoing implementation of the approved Mifepristone REMS Program. For example, consistent with the approved REMS, the *Patient Agreement Form* does not require the certified prescriber's signature, but rather the signature of the healthcare provider counseling the patient on the risks of mifepristone. Additional changes were made globally to provide consistency and clarity of the requirements for certified prescribers and healthcare providers who complete tasks under the supervision of certified prescribers.

A certified prescriber may submit the *Prescriber Agreement Form* to an authorized distributor if the certified prescriber wishes to dispense or supervise the dispensing of mifepristone; this is consistent with the current requirements of the Mifepristone REMS Program. Additional requirements were

added to incorporate mifepristone dispensing by a certified pharmacy. If a healthcare provider wishes to prescribe mifepristone by sending a prescription to a certified pharmacy for dispensing, the healthcare provider must become certified by providing the pharmacy a *Prescriber Agreement Form* signed by the provider. A certified prescriber must also assess the appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy.

The NDC and lot number of the dispensed drug will be recorded in the patient's record when mifepristone is dispensed by or under the supervision of a certified prescriber, replacing the requirement that serial numbers from each package of mifepristone be recorded in the patient's record. If prescribers become aware of the death of a patient for whom the mifepristone was dispensed from a certified pharmacy, the prescribers will be required to obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy.

The following materials support prescriber requirements:

- *Prescriber Agreement Form* for Danco Laboratories, LLC
- *Prescriber Agreement Form* for GenBioPro, Inc.
- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

Although certain activities (review of the Patient Agreement Form with patients and answering any questions about treatment, signing, providing a copy to the patient and retaining the Patient Agreement Form, providing a copy of the Medication Guide, and ensuring any deaths are reported to the Mifepristone Sponsor, recording the NDC and lot number from drug dispensed from the certified prescriber or those under their supervision) may be conducted by healthcare providers under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. We agree with the additional language to further clarify that the certified prescriber must ensure the guidelines for use of mifepristone are followed.

As proposed, certified prescribers may either, 1) continue to submit the Prescriber Agreement Form to an authorized distributor if the certified prescriber is dispensing or supervising the dispensing of the drug (as already required in the REMS), or 2) if the drug will be dispensed from a certified pharmacy, submit the Prescriber Agreement Form to the certified pharmacy that will dispense the drug (as proposed in the modification). Regarding #2, the pharmacy can only fill prescriptions written by a certified prescriber.

Based on our review of the proposed changes, the review team finds it acceptable for prescribers to submit their Prescriber Agreement Form directly to the certified pharmacy. Although certified prescribers still have the option of in-person dispensing of the drug, not all prescribers may want to stock mifepristone. Typically due to the number of drugs that are available and the expense associated with stocking prescription medications intended for outpatient use, most prescribers do not stock many medications, if they stock medications at all.

The proposal to submit a Prescriber Agreement Form to a certified pharmacy provides another option for dispensing mifepristone. The burden of providing the Prescriber Agreement Form prior to or when the prescription is provided to a certified pharmacy does not create unreasonable burden for prescribers. The burden of prescriber certification has been minimized to the extent possible. The Prescriber Agreement Form is designed to require minimal time to complete and requires that the prescriber submit it to the authorized distributor once, and if the prescriber chooses to use a certified pharmacy to dispense mifepristone, they will need to submit the form to the certified pharmacy.

There is an additional requirement added for certified pharmacies and certified prescribers in the event that a patient will not receive their medication from the certified pharmacy within four calendar days of the pharmacy's receipt of the prescription (for example, if the medication is not in stock). In this circumstance, the pharmacy will be required to contact the certified prescriber to make them aware of the delay and will be required to obtain from the prescriber confirmation that it is appropriate to dispense mifepristone to the patient even though they will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy. This confirmation is intended to ensure timeliness of delivery in light of the labeled indication and gestational age. Additional details and rationale on the pharmacy requirements to dispense and ship drug in a timely manner are described in section 3.3.2.3.

If a certified prescriber becomes aware of a patient death that occurs subsequent to the use of mifepristone dispensed from a pharmacy, the certified prescriber must obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy. This information will be reported to the appropriate Mifepristone Sponsor in the same manner prescribers have done previously. This additional requirement to obtain the NDC and lot number from the pharmacy is needed to ensure consistent adverse event reporting when mifepristone is dispensed from a certified pharmacy.

Prescriber Agreement Form

The Sponsors' proposed changes to the *Prescriber Agreement Form* aligned with those described above. The proposed *Prescriber Agreement Form* explains the two methods of certification which are: 1) submitting the form to the authorized distributor and 2) submitting the form to the dispensing certified pharmacy. Further clarification was added that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification. The statement that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program was also added. The following statement was added to the form: "I understand that the pharmacy may dispense mifepristone made by a different manufacturer than that stated on the Prescriber Agreement Form." The account set up information was removed and replaced with prescriber information response fields.

***Reviewer Comment**: We agree with the Sponsors' proposal. Changes in the above prescriber requirements were incorporated in the Prescriber Agreement Form.*

3.3.2.2. Patient Requirements

The *Patient Agreement Form* was updated to clarify that the signatures may be written or electronic, to reorganize the risk information about ectopic pregnancy, and to remove the statement that the Medication Guide will be taken to an emergency room or provided to a healthcare provider who did not prescribe mifepristone so that it is known that the patient had a medical abortion with mifepristone.

The following materials support patient requirements:

- *Patient Agreement Form*

***Reviewer Comment:** We agree with the Sponsors' proposal.*

The Patient Agreement Form continues to be an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the

patient, to provide the patient with the Patient Agreement Form, and to have the healthcare provider and patient sign the Patient Agreement Form, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The form is signed by the patient and the provider and placed in the patient's medical record, and a copy is provided to the patient, to document the patient's acknowledgment of receiving the information from the prescriber. The Agency agrees that the further clarification that signatures can be written or electronic is appropriate for the continued use of the form.

The reference to ectopic pregnancy has been reorganized in the document since it is not a risk of the drug. The signs and symptoms of an untreated ectopic pregnancy that may persist after mifepristone use have been clarified in the section of the form that explains the signs and symptoms of potential problems that may occur after mifepristone use.

The review team agrees with removing the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion. Although this statement has been in the Medication Guide for a number of years, upon further consideration, the Agency has concluded that patients seeking emergency medical care are not likely to carry a Medication Guide with them, the Medication Guide is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

3.3.2.3. Pharmacy Requirements

The Sponsors proposed that certified pharmacies, in addition to certified prescribers and HCPs under the supervision of certified prescribers, can dispense mifepristone. In order for a pharmacy to become certified, the pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy. The Authorized Representative must certify that they have read and understood the Prescribing Information for mifepristone. Each location of the pharmacy must be able to receive *Prescriber Agreement Forms* by email and fax and be able to ship mifepristone using a shipping service that provides tracking information.

Additionally, each dispensing pharmacy location must put processes and procedures in place to fulfill the REMS requirements. Certified pharmacies must verify prescriber certification by confirming they have obtained a copy of the prescriber's signed *Prescriber Agreement Form* before dispensing. Certified pharmacies must dispense mifepristone such that it is received by the patient within four days from the day of prescription receipt by the pharmacy. If the pharmacy will not be able to deliver mifepristone to the patient within four days of receipt of the prescription, the pharmacy must contact the prescriber to confirm the appropriateness of dispensing mifepristone and document the certified prescriber's decision. The pharmacy must also record the NDC and lot number from each package of mifepristone dispensed in the patient's record, track and verify receipt of each shipment of mifepristone, dispense mifepristone in its original package, and only distribute, transfer, loan, or sell mifepristone to certified prescribers or between locations of the certified pharmacy. The pharmacy must also report any patient deaths to the prescriber, including the NDC and lot number from the package dispensed to the patient, and remind the prescriber of their obligation under the REMS to report patient deaths to the Sponsor that supplied the mifepristone; the certified pharmacy also must notify the Sponsor that supplied the mifepristone that the pharmacy submitted a report of a patient death to the prescriber and include the name and contact information for the prescriber as well as the NDC and lot number of the dispensed

product. Record-keeping requirements of the pharmacy include records of *Prescriber Agreement Forms*, mifepristone dispensing and shipping, and all processes and procedures and compliance with those processes and procedures. Pharmacies must train all relevant staff and participate in compliance audits. Pharmacies must also maintain the identity of patients and providers as confidential, including limiting access to patient and provider identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes. The requirement that mifepristone not be dispensed from retail pharmacies was removed.

The following materials support pharmacy requirements:

- *Pharmacy Agreement Form* for Danco Laboratories, LLC
- *Pharmacy Agreement Form* for GenBioPro, Inc.

Reviewer Comment: *We agree with the Sponsors' proposal. The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, mifepristone can be dispensed from a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that the prescriber is certified prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the Patient Agreement Form is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review and our consideration of the distribution model implemented by the Sponsors during the periods when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients.*

The requirement to maintain confidentiality, including limiting access to patient and provider identity only to those personnel necessary for dispensing under the Mifepristone REMS Program or as necessary for payment and/or insurance purposes, is included to avoid unduly burdening patient access.

The Sponsors proposed inclusion of this requirement because of concerns that patients may be reluctant or unwilling to seek to obtain mifepristone from pharmacies if they are concerned that confidentiality of their medical information could be compromised, potentially exposing them to intimidation, threats, or acts of violence by individuals opposed to the use of mifepristone for medical abortion.[e] *Further, unwillingness on the part of prescribers to participate in the Mifepristone REMS Program on the basis of*

[e] See e.g., *2020 Violence and Disruption Statistics,* National Abortion Federation (Dec. 16, 2021), https://prochoice.org/national-abortion-federation-releases-2020-violence-disruption-statistics/; Amanda Musa, CNN, *Wyoming Authorities Search for a Suspect Believed to Have Set an Abortion Clinic on Fire*, CNN WIRE (June 10, 2022), https://abc17news.com/news/2022/06/10/wyoming-authorities-search-for-a-suspect-believed-to-have-set-an-abortion-clinic-on-fire/.

similar confidentiality concerns may unduly burden patient access by limiting the number of prescribers who are willing to send prescriptions to certified pharmacies. Addition of this requirement protects patient access by requiring the pharmacy to put processes and procedures in place to limit access to confidential information to only those individuals who are essential for dispensing mifepristone under the Mifepristone REMS Program or as necessary for payment or insurance purposes. Inclusion of this requirement for certified pharmacies is consistent with the requirement in the current Mifepristone REMS Program, that distributors maintain secure and confidential records.

Reference to mifepristone not being available in retail pharmacies was removed from the REMS. There is no single definition of the term "retail pharmacy" and therefore the scope of the exclusion in the REMS was not well defined. Including a restriction in the Mifepristone REMS Program that retail pharmacies cannot participate in the REMS may unintentionally prohibit the participation of mail order and specialty pharmacies that could, under one or more definitions, also be considered a "retail pharmacy."

After reconsideration of the term, "retail," the Agency concluded that a more appropriate approach was to articulate the specific requirements that would be necessary for pharmacy certification. As modified, the REMS will not preclude the participation of any pharmacy that meets the certification requirements. However, we acknowledge that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS. The REMS requires that pharmacies dispense mifepristone only after verifying that the prescriber is certified. The REMS further requires that pharmacies be able to receive the Prescriber Agreement Forms by email and fax. (b) (4)

The pharmacy certification requirements include that the drug reach patients within four days of the certified pharmacy receiving the prescription. During the course of the review, the review team concluded that requiring medication delivery to the patient within four days of the pharmacy's receipt of a prescription is acceptable based on the labeled indication and literature,[13] while taking into account practical shipping considerations (e.g., shipping over weekends and holidays). For patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription, the pharmacy must notify the certified prescriber and the certified prescriber must determine if it is still appropriate for the certified pharmacy to dispense the drug. The pharmacy must document the certified prescriber's decision. A prescriber's confirmation that it is appropriate to dispense mifepristone when it will not be delivered to the patient within the allotted four days is intended to ensure timeliness of delivery in light of the labeled indication and gestational age.

Pharmacy Agreement Form

The proposed *Pharmacy Agreement Form* is a new form and is the means by which a pharmacy becomes certified to dispense mifepristone. The form, which is submitted by an authorized representative on behalf of a pharmacy seeking certification, outlines all requirements proposed above. Clarification is included in the form that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program, do not require pharmacy certification. Any new authorized representative must complete and submit the *Pharmacy Agreement Form*. Spaces for specific authorized representative information and pharmacy name and address are included. The completed form can be submitted by email or fax to the authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The Pharmacy Agreement Form aligns with the pharmacy requirements discussed above.*

3.3.2.4. Distributor Requirements

The Sponsors proposed that the distributors' processes and procedures in the approved Mifepristone REMS Program be updated to ensure that mifepristone is only shipped to clinics, medical offices and hospitals identified by certified prescribers and to certified pharmacies. Distributors will continue to complete the certification process for any *Prescriber Agreement Forms* they receive and also will complete the certification process for pharmacies upon receipt of a *Pharmacy Agreement Form*, including notifying pharmacies when they become certified. FDA was removed as a potential auditor for distributors.

Reviewer Comment: *We agree with the Sponsors' proposal. At this time, FDA does not audit distributors directly, it carries out inspections of Sponsors to monitor industry compliance with REMS requirements.*

3.3.3. REMS Sponsor Requirements

3.3.3.1. Sponsor Requirements to Support Prescriber Certification

The Sponsors proposed additions to this section of the REMS document, including that Sponsors will ensure prescribers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy, and that Sponsors will ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date. Sponsors will also ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*: (1) within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies, or (2) within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The requirement to confirm that the locations associated with the certified prescriber are current is parallel to the pharmacy requirement that the authorized representative's contact information is up to date. In determining the pharmacy requirement, which is necessary to ensure program compliance and is consistent with other approved REMS that include pharmacy certification, the Agency also concluded that a parallel requirement for certified prescribers should be added.*

With respect to recertification, it is important that active certified prescribers are informed of and agree to new REMS requirements to ensure the continued safe use of mifepristone. There is minimal burden to recertification and the timelines allow sufficient time to accomplish recertification.

3.3.3.2. Sponsor Requirements to Support Pharmacy Certification

The Sponsors proposed the addition of Sponsor requirements to support pharmacy certification and compliance, including ensuring that pharmacies are certified in accordance with the requirements in the Mifepristone REMS Program, de-certifying pharmacies that do not maintain compliance with the certification requirements, and ensuring that pharmacy certification can be completed by email and fax to an authorized distributor. Annually, the authorized representative's name and contact information will be verified to ensure it corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, a new authorized representative must certify for the pharmacy. All reference to the requirement in the 2021 Mifepristone REMS Program that mifepristone to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber, and not from retail pharmacies, was removed.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes are in line with the REMS Modification Notification letters sent December 16, 2021. Refer to section 3.3.2.3 Reviewer Comments on Pharmacy Certification for rationale for removing the statement that mifepristone is not distributed to or dispensed from retail pharmacies. Ensuring that the authorized representative's contact information is up to date is necessary to ensure that there is always a point person who is responsible for implementing the Mifepristone REMS Program in their pharmacy and can address any changes that are needed if pharmacy audits identify a need for improvement.*

3.3.3.3. Sponsor Implementation Requirements

The Sponsors proposed that they will ensure that adequate records are maintained to demonstrate that REMS requirements have been met (including but not limited to records of mifepristone distribution, certification of prescribers and pharmacies, and audits of pharmacies and distributors), and that the records must be readily available for FDA inspections. The distributor audit requirement was updated to audit new distributors within 90 calendar days of becoming authorized and annually thereafter (a one-time audit requirement was previously required). The Sponsors also proposed a pharmacy audit requirement whereby certified pharmacies that order mifepristone are audited within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter for pharmacies that ordered in the previous 12 months.

Reviewer's Comment: *We agree with the Sponsors' proposal.*

The number of pharmacies that will certify in the REMS is uncertain; therefore, to obtain a reliable sample size for the audits, the Sponsors will need to audit all certified pharmacies within 180 calendar days after the pharmacy places its first order and annually thereafter for pharmacies that have ordered mifepristone in the previous 12 months. Audits performed at 180 days should allow time for establishment and implementation of audit protocols and for the Sponsors to perform the audits. With the addition of more stakeholders (i.e., certified pharmacies), it is also necessary to audit distributors annually to ensure the REMS requirements are followed. The requirement to conduct audits annually may be revisited if assessment data shows that the REMS is meeting its goal.

3.4. REMS Assessment Timetable

The Sponsors proposed that assessments must be submitted one year from the approval of the modified REMS and annually thereafter, instead of every three years as per the previous requirement.

Reviewer's Comment*: We agree with the Sponsors' proposal. With the addition of new pharmacy stakeholders and removal of the in-person dispensing requirement, more frequent assessment after this REMS modification is needed to ensure REMS processes are being followed and that the REMS is meeting its goal. The requirement can be revisited at a later date if assessment data shows that the modified REMS is meeting its goal. The NDA applicant is required to submit assessment reports as outlined in the timetable for submission of assessments. These reports address requirements for the Mifepristone REMS Program. The Sponsors have indicated that some data will be submitted as separate reports when Sponsor-specific information is needed to address the assessment metrics.*

4. Supporting Document

The Sponsors' REMS Supporting Document was substantially updated to include information regarding the proposed modification under review. Background and rationale from the 12/16/21 REMS Modification Notification letters was included. An updated description of the REMS goal and the ETASU was also included to align with the changes in the REMS Document and provide further clarification. Further explanation of prescriber requirements and rationale for various pharmacy requirements was also included.

Regarding implementation of the modified REMS, the Sponsors additionally proposed that pharmacies that received and shipped mifepristone during the Agency's exercise of enforcement discretion during the COVID-19 PHE, that wish to continue to dispense mifepristone, will be required to comply with the pharmacy certification requirements within 120 days of approval of the modified REMS.

The communication strategy to alert current and future prescriber and pharmacy stakeholders was outlined. Distributors, certified prescribers that purchased mifepristone in the last twelve months, and various professional organizations will receive information about REMS changes within 120 days of modification approval. The Sponsors proposed to list pharmacies that agree to be publicly disclosed on their respective product websites but disclosure of this nature is not a requirement of the REMS. The Sponsors indicated that they anticipate certified pharmacies that do not agree to public disclosure will communicate with the certified prescribers they wish to work with.

The REMS Assessment Plan is discussed in the following section.

Reviewer's Comment*: We agree with the Sponsors' proposal. The Supporting Document addresses all REMS requirements and provides sufficient clarification of implementation and maintenance of the REMS. The implementation requirements for pharmacies currently dispensing mifepristone under FDA's exercise of enforcement discretion during the COVID-19 PHE provide for continued use of these pharmacies without breaks in service. The communication strategy is also adequate given the efforts to reach both established certified prescribers and potentially new prescribers through professional organizations.*

The Sponsors' plan to communicate which pharmacies are certified to certified prescribers is adequate. For the reasons listed in section 3.3.2.3, confidentiality is a concern for REMS stakeholders. Disclosure of pharmacy certification status should be a choice made by individual certified pharmacies. The Sponsors have indicated that there will be some certified pharmacies that have agreed to publicly disclose their status, making this information available to certified prescribers who wish to use a pharmacy to dispense mifepristone.

5. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter.

The REMS Assessment Plan was revised to align with the modified REMS goal and objectives.

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

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

b. Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

c. Informing patients about the risk of serious complications associated with mifepristone.
    - This objective will be indirectly assessed using REMS Certification Statistics to avoid compromising patient and prescriber confidentiality. As part of the certification process, healthcare providers agree to:
        - Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained
        - Ensure that the *Patient Agreement Form* is signed by the healthcare provider and the patient
        - Ensure that the patient is provided with a copy of the *Patient Agreement Form* and the Medication Guide
        - Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record

The following revisions were made from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval letter:

The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.

REMS Certification Statistics metrics were added to capture certification numbers for program stakeholders to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. The total number of certified prescribers who certified with the wholesaler/distributor and the total number of certified prescribers who submitted a *Prescriber Agreement Form* to certified pharmacies were added to capture the additional method of prescriber certification. The number of newly certified prescribers and the number of active certified prescribers (i.e., those who ordered mifepristone or submitted a prescription during the reporting period) were added. Metrics were also added to capture the total number of certified, newly certified, and active certified pharmacies as well as the total number of authorized, newly authorized, and active authorized wholesaler/distributors.

Drug Utilization Data metrics were added to obtain information on shipment and dispensing of mifepristone. Metrics were added to capture the total number of tablets shipped by the wholesaler/distributor and the number of prescriptions dispensed.

REMS Compliance Data metrics were added to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. These metrics capture program deviations and evaluate overall if the REMS is operating as intended. Metrics include certified pharmacies and wholesaler/distributor audit results and a summary of instances of non-compliance and actions taken to address non-compliance. Prescriber compliance metrics were added to assess if prescribers are decertified along with reasons why. Pharmacy compliance metrics were added to assess if prescriptions were dispensed that were written by non-certified prescribers or if mifepristone tablets were dispensed by non-certified pharmacies as well as the number of pharmacies that were decertified along with reasons why. Wholesaler/distributor metrics were added to assess if shipments were sent to non-certified prescribers and non-certified pharmacies and corrective actions taken. The audit plan and non-compliance plans will be submitted for FDA review within 60 days after the REMS modification approval.

The Sponsors were asked to develop an assessment of prescription delivery timelines to determine what percentage of prescriptions were delivered on time (within four calendar days) and what percentage were delivered late (more than four calendar days) along with the length of the delay and reasons for the delay (e.g., mifepristone is out of stock shipment issues, other). The protocol for this assessment will be submitted for FDA review within 60 days after the REMS modification approval.

The revised REMS Assessment Plan is in the Appendix.

Reviewer's Comment*: We agree with the Sponsors' proposed REMS Assessment Plan.*

6. Discussion

The Sponsors submitted changes to the REMS to remove the requirement that mifepristone be dispensed only in certain healthcare settings (i.e., the "in-person dispensing requirement") and to add that certified pharmacies can dispense the drug in order to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. The REMS goal was updated to this effect. Changes were required for prescriber requirements and Sponsors to support the change in ETASU, and new pharmacy requirements were introduced.

The qualifications to become a certified prescriber have not changed as a result of the modification to the Mifepristone REMS Program; however, clarification has been provided for certain prescriber requirements and new prescriber requirements have been added to support pharmacy dispensing. Although certain responsibilities may be conducted by staff under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. In order to clarify this, revisions were made throughout the prescriber requirements and REMS materials to reflect that the certified prescriber is responsible for ensuring that the prescriber requirements are met. Additionally, the review team finds it acceptable that certified prescribers who wish to use a certified pharmacy to dispense mifepristone submit their *Prescriber Agreement Form* to the dispensing certified pharmacy (b) (4) . The burden to prescriber and

pharmacy stakeholders of having certified prescribers submit the form directly to the certified pharmacy that will be dispensing the mifepristone is not unreasonable and has been minimized to the extent possible; it does not impact the safe use of the product. Prescriber requirements necessitated by the addition of some pharmacy requirements were added as well and include prescriber responsibilities in deciding whether or not mifepristone should be dispensed if the patient will receive the drug from the certified pharmacy more than four days after the pharmacy receives the prescription, and prescriber adverse event reporting requirements if a prescriber becomes aware of a patient death and the mifepristone was dispensed from a certified pharmacy. The addition of the latter requirements will ensure consistent adverse event data is relayed to the relevant Mifepristone Sponsor.

Changes were made to the *Patient Agreement Form.* Changes to the form were added to improve clarity of the safety messages. After further consideration, the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion has been removed from the *Patient Agreement Form*. The Medication Guide is not typically carried by patients and this information can be obtained at the point of care. Changes align with updates to labeling submitted with this modification.[13, 14]

The Agency and Sponsors agreed during this modification to focus on certification of pharmacies that can receive *Prescriber Agreement Forms* via email or fax to complete the prescriber certification process. The proposed pharmacy certification requirements also support timely dispensing of mifepristone. If the mifepristone is shipped to the patient, the REMS requires that it must be delivered within four calendar days from the receipt of the prescription by the pharmacy; if the patient will receive the mifepristone more than four calendar days from pharmacy receipt of prescription, the REMS requires the pharmacist to confirm with the certified prescriber that it is still appropriate to dispense the drug to the patient. This allows prescribers to make treatment decisions based on individual patient situations. A requirement to maintain confidentiality was also added to avoid unduly burdening patient access since patients and prescribers may not utilize pharmacy dispensing if they believe their personal information is at risk. Ultimately, the addition of pharmacy distribution with the proposed requirements will offer another option for dispensing mifepristone, alleviating burden associated with the REMS.

(b) (4)

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The Agency reviewed the REMS in 2021, and per the review team's conclusions, a REMS modification was necessary to remove the in-person dispensing requirement and add a requirement that pharmacies that dispense the drug be specially certified; the review team concluded that these changes could occur without compromising patient safety. There have been no new safety concerns identified relevant to the REMS ETASUs that the applicants proposed modifying in their June 22, 2022 submissions since the REMS Modification Notification letters dated 12/16/2021. It is still the position of the review team that the proposed modification is acceptable.

Because the modification proposed include changes to the ETASU of the Mifepristone REMS Program, the assessment plan and timetable of assessments were changed. The assessment plan will capture information on pharmacy dispensing and provide valuable insight as to whether the program is operating as intended Annual assessments are consistent with other approved REMS modifications for major modifications necessitating extensive assessment plan changes.

As part of the REMS Assessment Plan, the REMS goal and objectives are assessed using Program Implementation and Operations Metrics, including REMS Certification Statistics and REMS Compliance Data. The metrics will provide information on the number of certified prescribers, certified pharmacies, and authorized wholesalers/distributors as well as if mifepristone is dispensed by non-certified prescribers or pharmacies. The Sponsors will use the indirect measure of healthcare provider certification to address the objective of informing patients of the risk of serious complications of mifepristone, due to concerns with prescriber and patient confidentiality. Although we typically assess whether patients are informed of the risks identified in a REMS through patient surveys and/or focus groups, we agree that the Sponsors' continued use of the indirect measure of healthcare provider certification adequately addresses the Mifepristone REMS Program objective of informing patients. In addition, because of these prescriber and patient confidentiality concerns, we believe it is unlikely that the Agency would be able to use the typical methods of assessment of patient knowledge and understanding of the risks and safe use of mifepristone.

7. Conclusions and Recommendations

The review team finds the proposed REMS modification for the Mifepristone REMS Program, as submitted on June 22, 2022, and amended on October 19, 2022 (Danco) and October 20, 2022 (GBP), November 30, 2022 (both), December 9 (both), and December 16 (both) acceptable. The REMS materials were amended to be consistent with the revised REMS document. The review team recommends approval of the Mifepristone REMS Program, received on June 22, 2022, and last amended on December 16, 2022, and appended to this review.

8. References

1. (b) (6) Clinical Review of SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909590.

2. (b) (6) Summary Review for Regulatory Action for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909594.

3. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909588.

4. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909587.

5. Approval Letter for SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909592.

6. (b) (6) REMS Review for mifepristone, NDA 020687. February 22, 2018. DARRTS Reference ID: 4224674.

7. Approval Letter for SE-20 REMS Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 4418041.

8. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the

Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

9. (b) (6) REMS Modification Rationale Review for mifepristone, NDA 020687. December 16, 2021. DARRTS Reference ID: 4905882.

10. General Advice Letter for the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, NDA 020687, April 15, 2022. DARRTS ID 4969358.

11. Format and Content of a REMS Document Guidance for Industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf. Accessed on December 18, 2022.

12. Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2022; 107:36-41. https://doi.org/10.1016/j.contraception.2021.09.008. This article was included in the literature review for the December 16, 2021 REMS Modification Rationale Review, while the article was still in press.

9. Appendices

REMS Document

Prescriber Agreement Form for Danco Laboratories, LLC

Prescriber Agreement Form for GenBioPro, Inc.

Patient Agreement Form

Pharmacy Agreement Form for Danco Laboratories, LLC

Pharmacy Agreement Form for GenBioPro, Inc.

Mifepristone REMS Assessment Plan

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.

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

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]

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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(b) (6)

01/03/2023 05:33:47 PM

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]
	[redacted]
	[redacted]
	[redacted]
Review Completion Date	December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

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EXECUTIVE SUMMARY

This review provides the [redacted] rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the "in-person dispensing requirement" for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[a] This review provides the analysis of the [redacted] ([redacted] and the [redacted] ([redacted] 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 (b) (4)

[k] FDA General Advice Letter for NDA 20687, April 12, 2021.
[l] FDA General Advice Letter for ANDA 091178, April 12, 2021.

[m] NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.
[n] NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Mifeprex tablets to the distributor. [redacted] non-certified healthcare provider dispensed [redacted] to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed [redacted] shipments representing [redacted] tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The [redacted] ([redacted] conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.[o,p]

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

[redacted]. Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. [redacted] # 2007-525. Finalized April 12, 2021.

[redacted] Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. [redacted] # 2007-525. Finalized December 16, 2021.

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6)

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested[q] to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

[q] On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).[r]

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

[r] The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.[s]

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman[2], Wiebe[7], Rocca[6]) and dispensing mifepristone from pharmacies by mail (Grossman[1], Upadhyay[14], Hyland[15]). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond[16], Chong[3], Anger[17]], Kerestes[4], Aiken[5] (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright[18]). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken[19] (2017), Norton[20], Endler[21]). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman[2] conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

[s] The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca[6] conducted an observational study evaluating 605 participants at ≤63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion (>97%) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[7] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; ≥ 95% calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman[2]), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe[7]) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service[t] which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca[6] study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman[1] published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

[t] As noted in Mark[23] and Martin[24], most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay[14] reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[15] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up". The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman[1] study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland[15] study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay[14] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.[3,4,5,16,17] Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

exclusively: Raymond[16] from May 2016 to December 2018, Chong[3] from May 2016 to September 2020 and Anger[17] from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,[4] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken[5] (2021).

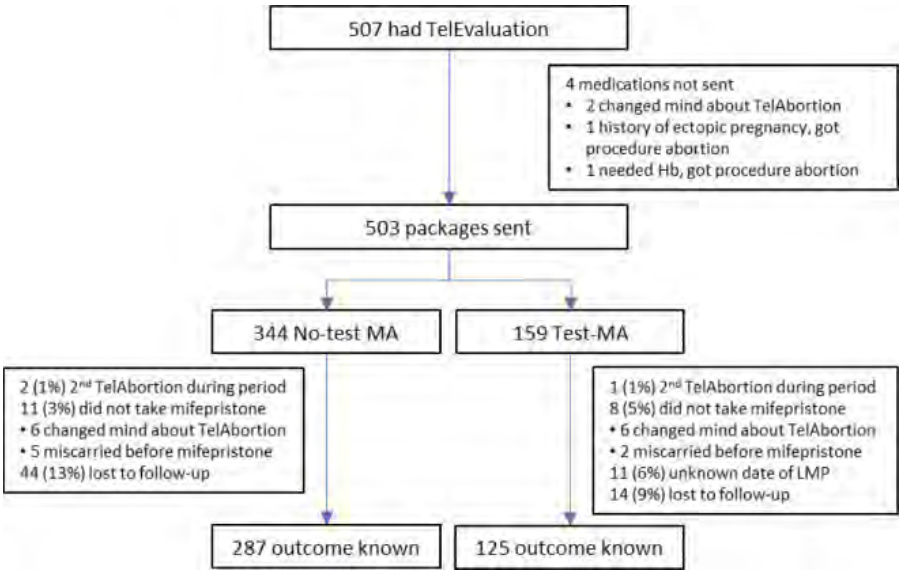
Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond[16] (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.[16] All participants received medications within 8 days.

Chong[3] updated the findings from the Gynuity study described in Raymond[16] and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger[17] compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"[u] based on a sample protocol published by Raymond[22] (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

[u] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.[22]



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes[4] was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports[3,16,17] and Kerestes[4] support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond[16], Chong[3]) and Kerestes[4] report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken[5] (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion[u] (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken[5] (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),[3,16,17] Kerestes[4], and Aiken[5] (2021) support that efficacy of medical abortion was maintained. The Aiken[5] study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond[16] Chong[3], and Kerestes[4] all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's[17] comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond[16] publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond[16] reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright[18] reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken[5] (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail.[v] Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken[19] (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort's GA (almost 80% less than 7 weeks, labeled success for medical abortion ≤ 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants' self-reporting.

[v] In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Endler[21] and Norten[20] have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler[21] compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the "first or second day of abortion" that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten[20] describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken[19] (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.[w]

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

[w] *The Patient Agreement Form* can be signed in person or through other means.

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications[x] that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by "partner organizations". The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

[x] The 15 publications correspond to endnote numbers: 1-7, 14-21.

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond[16], Chong[3], Anger[17] and Kerestes[4]), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond[16]), may be associated with participants being located significant distances from their providers. The Aiken[5] (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman[1] and Hyland[15], where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's[1] interim analysis found no increases in SAEs. Hyland[15] reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.[j,y,z] Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

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) (4) 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) (4) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

[aa] Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

6. References

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7. Appendix A

References Cited in Letters from Plaintiffs

References cited in letter from *Chelius v. Becerra* Plaintiffs (September 29, 2021)	
References included in the REMS review	
Aiken A et al. BJOG 2021: 128 (9): 1464-1474	
Chong, et al. Contraception 2021; 104(1) 43-48	
Daniel S. et al. Contraception 2021; 104(1): 73-76	
References excluded from the REMS review	**Rationale for Exclusion**
Am. Coll. of Obstetricians & Gynecologists, *Position Statement: Improving Access to Mifepristone for Reproductive Health Indications* (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications	Policy/advocacy statement
House of Delegates, Am. Med. Ass'n., *Memorial Resolutions Adopted Unanimously No. 504 (2018)* https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf	Policy/advocacy statement
Cong. Of Delegates, Am. Acad. Of Fam. Physicians, *Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization of Mifepristone* (May 24, 2018) https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf	Policy/advocacy statement
Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625 Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96 Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235 Barr-Walker J, et al PLoS One 2019;14(4): e0209991 Grossman et al JAMA Network 2017;317(4):437, 437-438 Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244 Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262 Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232 Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689	Focused on the logistics of accessing abortion care.
CDC MMWR Abortion Surveillance – United States, 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down	Contains primarily general statistics on abortion care by state.

References cited in appendix from *Chelius v. Becerra* Plaintiffs (September 29, 2021)
References included in the REMS review
None

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

References cited in letter from Society of Family Planning (August 11, 2021)
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)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

DATE: March 28, 2016

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

THRU: (b) (6)

TO: (b) (6)

RE: NDA 020687, Supp 20

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

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

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

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/s/

(b) (6)

03/29/2016

adding to for the record

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

[redacted]

Date: March 29, 2016

[redacted]

Subject: [redacted] 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

[redacted] Review Division: [redacted]

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.

---

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

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/s/

(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)

(b) (6)

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] 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 [redacted] (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

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

DANCO

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

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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

- [redacted] Mifeprex Post-marketing Safety Review: dated August 20, 2015
- Addendum to [redacted] Review of Year 4 REMS Assessment Report: dated March 29, 2016
- [redacted] 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 "[redacted] 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, [redacted] 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 [redacted] 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, [redacted] 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 [redacted] 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:

---

[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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/s/

(b) (6)

03/29/2016

(b) (6)

03/29/2016

Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK MANAGEMENT REVIEW

Date:	January 27, 2012
Risk Management Analyst:	Suzanne Robottom, Pharm.D. Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D., DRISK
Division Director:	Claudia Karwoski, Pharm.D., DRISK
Drug Name:	Korlym (mifepristone)
Dosage and Route:	300 mg tablets; by mouth
Application Type/Number:	NDA 202-107
Applicant/sponsor:	Corcept
OSE RCM #:	2011-2351

EXECUTIVE SUMMARY

The purpose of this review is to document DRISK's determination that a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) is not necessary for the approval of mifepristone for the treatment of the signs and symptoms of endogenous Cushing's syndrome.

Corcept submitted a 505(b)(2) application for approval of Korlym (mifepristone) for the treatment of the signs and symptoms of endogenous Cushing's syndrome. Mifepristone (Mifeprex) is currently approved for pregnancy termination with a REMS with ETASU. Based on FDA feedback provided at the September 14, 2010 pre-NDA meeting, Corcept proposed a REMS with ETASU with their NDA submission.

After extensive research and multiple discussions with the review team, DRISK and the Division of Metabolism and Endocrinology Products (DMEP) determined that:

- A REMS with ETASU is not necessary to ensure that the benefits outweigh the risks of Korlym *in the Cushing's population*.
- A REMS with ETASU for Korlym would not improve the benefit/risk balance for the intended use (Cushing's) population and would add burden.
- Use of Korlym outside of Cushing's syndrome cannot be prospectively quantified.

The REMS Oversight Committee and the Center Director provided additional guidance and affirmed that although a REMS is required for Mifeprex, a REMS for Korlym is not necessary to ensure that the benefits of the drug outweigh its risks at this time. Korlym's safety and drug utilization should use be monitored through post marketing requirements (PMR). If data indicate that the current approach compromises the integrity of the Mifeprex REMS and results in serious adverse events, or additional serious safety signals arise, further regulatory action must be considered.

1 INTRODUCTION

The purpose of this review is to document DRISK's determination that a REMS with ETASU is not necessary for the approval of mifepristone for the treatment of the signs and symptoms of endogenous Cushing's syndrome.

1.1 BACKGROUND

Corcept submitted a 505(b)(2) application on April 15, 2011 for approval of Korlym (mifepristone) to treat the clinical and metabolic effects of hypercortisolism in adult patients (≥ 18 years of age) with endogenous Cushing's syndrome including:

- Patients with Cushing's disease who have not adequately responded to or relapsed after surgery
- Patients with Cushing's disease who are not candidates for surgery

(b) (4)

Korlym is manufactured as 300 mg tablets. The proposed dosing for the aforementioned indication is 300 to 1200 mg daily by mouth.

1.2 REGULATORY HISTORY

Mifepristone if currently marketed as Mifeprex and approved on September 28, 2000 under 21 CFR 314 Subpart H for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The approved dosing is 600[1] mg (three (3), 200 mg tablets) followed by misoprostol on Day 4. Since approval, mifepristone is available only through a restricted distribution program that requires prescribers to be enrolled to be able to order Mifeprex and should only be distributed to/through a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. Mifeprex is not distributed to or dispensed through retail pharmacies. The restricted distribution program was approved as a REMS on June 8, 2011.[2]

In 2007, Corcept initiated a clinical development program to evaluate the clinical benefit of mifepristone in patients with Cushing's syndrome and received orphan drug designation on July 5, 2007.

A pre-NDA meeting with Corcept was held on September 14, 2010. Corcept informed the FDA that they intended to submit a REMS and requested comments on the draft REMS. The FDA informed Corcept that for this NDA/indication, a REMS with restricted distribution would be necessary to address the risk of termination of pregnancy. The proposed REMS must be sufficient to maintain the integrity of the current Mifeprex restricted distribution program. The sponsor was instructed that a complete review of the proposed REMS, and REMS materials would be done in conjunction with the full clinical review after the NDA is submitted.

On April 15, 2011 Corcept submitted NDA 202107 for review with a proposed REMS.

2 MATERIALS REVIEWED

The following materials were reviewed:

- Weber J. Pre-NDA Meeting Preliminary Comments for September 14, 2010. Signed under IND 76480 on September 9, 2010 by Weber J.
- NDA 202107 submitted on April 15, 2011 and received on April 18, 2011 with a proposed REMS with ETASU.
- Bhatnagar U. Maternal Health Team review for Mifepristone. Signed September 15, 2011 by Bhatnagar U, Feibus K, and Mathis L.
- Greene P. Drug use review of Mifeprex. Signed September 19, 2011 by Greene P, Chai G, and Governale L.

[1] Standard practice is to dispense a single, 200 mg tablet of mifepristone, not 600 mg. In addition, the standard misoprostol dose is 800μg (4 tablets), not 400 μg.
[2] Mifepristone was included on the list of 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 with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

- November 3, 2011 Center Director Briefing on Mifepristone for Cushing's syndrome. Signed into DAARTS for NDA 202107 on November 15, 2011 by Egan A.
- (b) (6) Division of Reproductive and Urology Products consult response. Signed November 18, 2011 by (b) (6).

3 RISK BENEFIT CHARACTERIZATION

3.1 CUSHING'S SYNDROME AND TREATMENT OPTIONS

Cushing's syndrome is a serious, multisystem disorder that results from overproduction of cortisol by the adrenal glands. For those not cured by surgery, it is a chronic and debilitating condition.[4] If left untreated, Cushing's syndrome limits survival to 4 to 5 years following initial diagnosis.[3]

Surgical resection of the offending tumor remains first line treatment, and initial cure or remission is obtained in 65-85% of patients with Cushing's disease.[4] In cases that surgery only partially or temporarily controls glucocorticoid hypersecretion (or for patients who are not candidates for surgery),[5] radiation and/or pharmacologic treatment is used for disease control. A two to three fold increase in mortality is observed in most studies and this excess mortality seems confined to patients in whom initial cure was *not* obtained (the indicated population for mifepristone).[4]

There is an unmet medical need for additional drug treatment options for Cushing's syndrome. The following table lists the drug treatment options, none of which are approved for Cushing's syndrome:[2,6]

Steriodogenic inhibition	**Adrenolytic**	**Neuromodulators of ACTH release**	**Glucocorticoid receptor antagonism**
• Metyrapone (not available in US) • Aminoglutethimide (discontinued)^ • Ketoconazole	• Mitotane^^ • Etomidate	• Cyproheptidine* • Bromocriptine* • Valproic acid* • Octreotide*	• Mifepristone
^Aminogluthethimide was approved in 1980 and indicated "for the the suppression of adrenal function in selected patients with Cushing's syndrome." ^^Mitotane was approved in 1970 and indicated for "the treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types." *Agent has not demonstrated consistent clinical efficacy.[3]			

[3] Gums JG, Smith JD. Adrenal Gland Disorders. Pharmacotherapy: A pathophysiologic approach. 4th ed. Ed Dipiro JT. Stamford, Appleton & Lange, 1999. Print.
[4] Steffensen C, Bak AM, Rubeck KZ, Jorgensen JO. Epidemiology of Cushing's syndrome. Neuroendocrinology 2010;92(supp 1):1-5.
[5] Johanssen S. Allolio B. Mifepristone (RU 486) in Cushing's syndrome. Euro J Endocrin (2007)156; 561-569.
[6] Heyn J, et al. Medical suppression of hypercortisolemia in Cushing's syndrome with particular consideration for etomidate. Pituitary (online May 10, 2011).

3.1.1 Size of Population

Cushing's syndrome is a rare disorder with incidence ranging from 0.7 to 2.4 per 1 million persons per year.[7] Ninety percent of all cases of Cushing's syndrome occur during adulthood; the incidence of Cushing's syndrome in children is estimated at approximately 0.2 cases per 1 million persons per year.

It is estimated that at any given time there are approximately 20,000 patients with Cushing's syndrome in the U.S. The peak incidence of Cushing's syndrome due to an adrenal or pituitary tumor occurs in persons 25-40 years of age; females are 8 times more likely than males to develop hypercortisolemia from a pituitary tumor and 3 times more likely to develop a cortisol-secreting adrenal tumor.

In the US, it is estimated that approximately 5,000 patients would be considered candidates for treatment with Korlym.

3.2 EXPECTED DRUG BENEFIT

Mifepristone works by binding to glucocorticoid receptors, preventing cortisol from binding, and thereby blocking cortisol's activity and effects. It does not decrease the amount of circulating cortisol. It has a rapid onset of action (~90 minutes for peak plasma concentrations).

According to the sponsor in Study 400 (open label, 24 week prospective trial), 60% of the diabetes patients met the primary endpont of at least a 25% reduction in $AUC_{glucose}$, and antidiabetic medication use was reduced in half of the patients. The Data Review Board determined that 72% of patients met the secondary endpoint of a change in signs and symptoms at week 24.

Mifepristone may be used as an adjunct to radiation, palliative treatment, or when rapid onset of anti-glucocorticoid effect is required (e.g., psychosis).

3.3 DURATION OF TREATMENT

Cushing's syndrome that is not cured by surgery is a chronic condition. Patients may be treated indefinitely (weeks, months, years/decades) with mifepristone.

3.4 SEVERITY OF THE RISK

The observed risks (adverse events documented in the safety database; adrenal insufficiency, hyopkalemia, and endometrial hyperplasia) in patients with Cushing's syndrome were considered. After discussion with DMEP, we agree that these risks can be adequately addressed through labeling.

[7] Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006 May 13;367 (9522):1605-17.

Two risks were identified that are anticipated to occur in the post-marketing setting. These risks were the focus of the risk management discussion.

3.4.1 Fetal Loss (unintended pregnancy termination)

3.4.1.1 Cushing's Syndrome Patients

Mifepristone blocks progesterone receptors at lower doses than necessary for glucocorticoid receptor inhibition. Therefore, the lowest treatment dose studied for the treatment of Cushing's syndrome is effective for terminating pregnancy. However, mifepristone alone is less effective for pregnancy termination when compared to the combined regimen mifepristone/prostaglandin.[8]

Women with Cushing's syndrome are not at substantial risk for fetal loss because they are unlikely to be pregnant. The review by the Maternal Health Team (MHT) states that amenorrhea and ovulatory disturbances are associated with untreated Cushing's syndrome and therefore pregnancy occurs "rarely" in this population. Pregnancy may occur in a small subset of patients with Cushing's syndrome who are of childbearing age. MHT recommends that this possibility be noted in labeling.[9]

At the time treatment is initated with mifepristone, a woman has a low likelihood of conception due to her underlying disease. During treatment, if she is not compliant with mifepristone treatment, she would be amenorrheic due to worsened disease condition. If she is compliant with medication, mifepristone would prevent a sustained pregnancy. Therefore, the risk of fetal loss before and during treatment in the intended patient population appears low.

Pregnancy tests were performed in Study 400 as part of enrollment and repeated after any significant interruption of treatment. No pregnancies were reported.

3.4.1.2 Non-Cushing's Syndrome Patients

There are a variety of uses for mifepristone (b) (4). It has been studied to treat the following:

(b) (4)

(b) (4).

[8] (b) (6) Division of Reproductive and Urology Products consult response. Signed November 18, 2011 by (b) (6).

[9] Bhatnagar U. Maternal Health Team review for Mifepristone. Signed September 15, 2011 by Bhatnagar U, Feibus K, and Mathis L.

At present, mifepristone is only commercially available in blister packages (3 pills per carton) that are sold through the Mifeprex REMS. If Korlym is approved without restrictions (e.g. REMS), mifepristone will be more readily available to treat females of child bearing potential with other chronic conditions. The extent of off-label use of mifepristone, for the above conditions, in the post-marketing setting is unknown.

3.4.2 Intended Termination of Pregnancy with Korlym

If Korlym is approved without a REMS with restricted distribution, there will be increased access to mifepristone. This could lead to 1) prescribers prescribing Korlym for the termination of pregnancy without following the safeguards that are in place for Mifeprex and/or 2) misuse, pilfering, and diversion of Korlym for the termination of pregnancy not under the supervision of a healthcare provider.

The risk mitigation tools for the Mifeprex REMS are physician certification and controlled access to assure safe use. A Mifeprex prescriber must agree that he/she meets the required qualifications to assure the drug is used safey and appropriately. Compliance with the REMS requirements is not enforced beyond a one-time completion of the enrollment form (e.g., signed Patient Agreements are not collected). The certification requirement is the tool that provides controlled access for Mifeprex. Without restricted distribution, a prescriber using Korlym for pregnancy termination would not have to attest to having certain skills, agree to document certain information/activities, or report adverse events. The patient would not receive a Patient Agreement or Mifeprex Medication Guide that would provide the most relevant and important information to her for pregnancy termination. The current REMS does not prevent use beyond 49 days gestation, termination of an ectopic pregnancy, bleeding, incomplete abortion, and infection.

In considering if there is increased potential for pilfering and misuse with Korlym, we note that Mifeprex is distributed only to medical facilities and dispensed to the patient in small quantities (a single tablet) by certified prescribers. Korlym will be distributed directly to patients, in larger quantities and each Korlym tablet is an effective dose for pregnancy termination. Moreover, Korlym is proposed to be packaged in bottles of 28 and 280, making diversion and pilfering presumably easier relative to the Mifeprex packaging. Similar to Korlym, there is potential for Mifeprex to be pilfered or diverted from a distribution facility, during shipping, or at the place of dispensing. Mifeprex has processes in place to prevent drug loss during distribution and shipping that can be done outside a REMS for Korlym. It is not known if clinics keep careful stock and dispensing records of Mifeprex.

3.5 Risk in Context of Drugs in Class and Among Other Drugs Used to Treat the Disease

There are no other glucocorticoid receptor antagonists approved in the U.S. for comparison.

Ketoconazole, metapyrone (not approved in U.S.), mitotane, etomidate are anti-corticolic drugs that are used for the treatment of Cushing's syndrome. Because these drugs have a

different mechanism of action, they are not associated with the same potential risks as mifepristone. These drugs are associated with serious risk(s) although none of these drugs have a REMS.

3.6 How the Risk(s) are Managed Across Other Products and/or Diseases

3.6.1 Fetal Loss

Other drug products are associated with fetal loss (e.g., methotrexate, misoprostol; see Attachment 1). At present, this risk is addressed through labeling for these drugs. There are no REMS approved that address only fetal loss without also the accompanying risk of birth defect.

3.6.2 Intended Termination of Pregnancy with Korlym

We identified two drugs, misoprostol and methotrexate, that are associated with a risk of pregnancy termination and are approved for other uses. See the table in Attachment 1. The extent to which misoprostol and methotrexate are used off-label to terminate pregnancy is unknown. With each drug, the risk of termination of pregnancy is managed through labeling (Contraindication, Boxed Warning) and neither product has a REMS.

3.6.3 Misuse

Misuse has been addressed in different ways as follows:

Voluntary Restricted Distribution:

- *Example: Egrifta/growth hormone*: Growth hormones are at risk for misuse and abuse. None of the growth hormone products have a REMS. However, the sponsor has voluntarily decided to distribute this product through a non-REMS restricted distribution system which allows tracking "of each box of Egrifta to determine the volume of product dispensed and evaluate if the projected number of boxes dispensed correlates with prescription use in the intended population."[10] Egrifta was approved in 2010 with no REMS and no PMR for monitoring drug use.

Required Restricted Distribution Program

- *Example: Xyrem*[11]
  - At the time Xyrem was initially approved in 2002, the Sponsor agreed as a condition of approval to distribute and dispense Xyrem through a primary and exclusive central pharmacy, implement a program to educate physicians and patients about the risks and benefits of Xyrem, fill the initial prescription only after the prescriber and patient received and read the educational materials, and maintain patient and prescribing physician registries.[12]

[10] LaCivita C. Review of REMS for Egrifta. Signed September 3, 2010.
[11] Xyrem was included on the list of 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 with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007.
[12] Choudhry Y. REMS Interim Comment Set #1. Signed August 1, 2011 by Choudhry Y and Worthy K.

3.6.4 Same Active Ingredient, Different Indication and Different Risk Management Approaches

The agency evaluates an active ingredient based on the risk benefit profile for the intended population. To date, the Agency has not required a REMS for a product based only on the fact that the active ingredient already has a REMS for one population. For example, denosumab was originally approved under two tradenames for different indications. Prolia was initially approved for the treatment for post-menopausal osteoporosis (PMO). At that time, a REMS for Prolia was required and approved consisting of a Medication Guide and communication plan to "inform healthcare providers about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw." Under the tradename Xgeva, denosumab was approved for prevention of skeletal-related events in patients with bone metastases from solid tumors. A REMS was not required given the resulting differences in the risk benefit profile when considering the patient populations (post-menopausal women vs cancer patients with bone metastases) and prescribing populations (internists vs oncologists).

3.7 PRODUCTS AFFECTED

Mifeprex (and pending generics) are potentially affected because they are or will only be available under a restrictive REMS.

4 RISK MANAGEMENT CONSIDERATIONS

The following factors are important to consider:

- Burden to the intended population

  It is important to ensure that the intended treatment population can receive Korlym in a timely, dependable manner in the least burdensome way. Any restrictions will impede access with little to no benefit to Cushing's syndrome population.

- Confidentiality/Privacy

  Confidentiality and patient privacy is a significant issue with Mifeprex. To what extent do stakeholders who make, distribute, dispense, prescribe, and use Korlym need protection from a confidentiality perspective?

  The purpose of a REMS is to ensure the benefits of the drug outweigh its risks. Confidentiality and concern regarding the safety of the prescribers, pharmacists, and patients does not meet criteria. Confidentiality can be maintained without a REMS. Privacy may be better maintained if there are no systems in place to track formally prescribers and patients. Risk to pharmacies that stock the drug should be considered but it is outside the purview of a REMS.

- Reproductive potential for various possible Korlym off-label use populations

As stated in section 3.4.1.2. above, there are a variety of uses for mifepristone (b) (4). The therapeutic areas included below are more likely to include females of reproductive potential than other uses (b) (4)). A formal epidemiologic review was not conducted to estimate of the proportion of females of reproductive potential for each use. However, the following observations and/or assumptions were made:

(b) (4)

The degree to which Korlym will be used off label for the above uses is unknown.

- Extent of current off-label use

  Current Mifeprex drug utilization information is not informative in predicting broader uses for Korlym. In the September 19, 2011 mifepristone drug use review using commercial databases was conducted, off-label use was described as "uncommon" based on information obtained through a *sample* of medical offices and outpatient clinics. Sales distribution data was not available. The lack of findings are not surprising given the design of the Mifeprex REMS.

5 RISK MANAGEMENT OPTIONS

DRISK analyzed more than six risk management options to address intended termination of pregnancy by:

- HCPs outside of Mifeprex REMS
- women who seek to terminate a pregnancy and are not under the care of an HCP

Ultimately, three options were considered.

1. No REMS and voluntary restricted distribution through specialty pharmacies/distributors

   This REMS option may minimize diversion and subsequent misuse by minimizing the number of pharmacies stocking and dispensing Korlym for outpatient use. This option is in alignment with DMEP and DRISK's assessment that a REMS is not necessary to assure the safe use of mifepristone for treating patients with Cushing's syndrome because we believe the likelihood that a Cushing's patient experiences "serious complications" relating to pregnancy termination are low.

This approach is also consistent with misoprostol and methotrexate, both of which are known abortifacents and do not have a REMS to address that risk. This approach is used to prevent misuse of the growth hormone products.

2. REMS with ETASU – dispensing through certified specialty pharmacies

This REMS option may minimize diversion and subsequent misuse by minimizing the number of pharmacies stocking and dispensing Korlym for outpatient use. In addition, Corcept would be required to provide FDA an assessment of how the REMS is achieving its goals.

This option does not address intended termination of pregnancy with Korlym.

3. REMS with ETASU – prescriber certification (agreement not to use for termination of pregnancy) and distribution through certified specialty pharmacies that are willing to track inventory

This REMS option would minimize diversion and subsequent misuse as described above. In addition, certified pharmacies (for outpatient dispensing, not inpatient hospital pharmacies) would verify that prescribers were certified. Prescriber certification would consist of agreement not use Korlym for pregnancy termination. The addition of prescriber certification would address the risk of intended termination of pregnancy with Korlym.

These options assume that the safety labeling is maximized to address Korlym use in pregnancy.

6 DISCUSSION

The issue of how to address intended termination of pregnancy was discussed at the REMS Oversight Committee meeting on September 29, 2011 and at a Center Director Briefing on November 3, 2011.

DMEP and DRISK presented at both meetings that women with Cushing's syndrome are unlikely to be or become pregnant given the effects of their disease on the reproductive system and the effects of daily mifepristone treatment. Therefore, addressing the risk of fetal loss associated with Korlym was not discussed because 1) pregnancy is not a likely event in the intended population and; 2) the use of Korlym for "off-label" uses (in women more likely to be pregnant) is unknown and available data do not indicate that mifepristone would be first line treatment for any diseases or conditions at this time. For these reasons, there was general agreement that fetal loss can be adequately addressed through labeling and is not necessary to require additional safe use measures through a REMS at this time.

The team stated that for any risk management approach, it is important to ensure that the intended treatment population can receive Korlym in a timely, dependable manner in the least burdensome way. Any restrictions could impede access without benefit to the intended population.

The primary focus shifted to whether or not a REMS is necessary for Korlym to maintain the integrity of the Mifeprex REMS. While the absence of any restrictions on Korlym could undermine the safe use conditions required by the Mifeprex REMS, a number of other factors are important considerations including:

- The burden (reduced access, treatment delays) of a restrictive REMS to the Cushing's population without any benefit from the REMS for this population.
- Overall drug exposure and subsequent access is anticipated to be small given the small size of the intended use population and lack of a signal for substantially broader use.
- The sponsor's plan to distribute Korlym through a specialty pharmacy regardless of the REMS. If necessary, this provides the sponsor the ability to monitor use more closely.
- The cost - If the cost of this orphan product is substanial, it may be expensive to obtain and deter use for pregnancy termination as well as other off label uses. In addition, third party payors/reimbursement may play a substantial role in influencing prescribing behavior. It is unknown how much Korlym will cost and how cost will impact prescribing behavior.[13]

The need for some monitoring of use was discussed. Commercial drug use databases will not provide FDA with adequate estimates of Korlym use because Korlym will be dispensed through a specialty pharmacy. As noted above, using a single specialty pharmacy does allow the sponsor the ability to monitor use more closely through its business contract with the specialty pharmacy. Similarly, commercial drug use databases are not able to provide an accurate estimate of Mifeprex use due to how it is distributed and dispensed. The first REMS assessment for Mifeprex is due June 2012 which we anticipate will provide a baseline to quantify current Mifeprex use. Given these considerations and the discussion with the Center Director, we agree that a post-marketing requirement (PMR) study to obtain Korlym use data (age, gender, dose, duration of treatment) "to better characterize the incidence rates of adverse events with Korlym" is prudent. Monitoring drug use data for both Mifeprex and Korlym, in conjunction with reports of serious adverse events resulting from pregnancy terminations outside of the Mifeprex REMS, will be important factors in future regulatory action to address any compromise to the Mifeprex REMS.

7 CONCLUSION

A REMS for Korlym is not necessary to ensure that the benefits of the drug outweigh its risks at this time. We agree that it is prudent to monitor use through a PMR. If data indicate that this approach compromises the integrity of the Mifeprex REMS and results in serious adverse events, or additional serious safety signals arise, further regulatory action must be considered.

ATTACHMENTS

[13] Planned parenthood charges $300-800 for a medical abortion (includes diagnostic testing, mifepristone, and misoprostol).

ATTACHMENT 1: Drugs with a risk associated with an off-label use

Drug	Abortifacient Efficacy	Indication	Off-label use*	Contraindication	Boxed Warning
Misoprostol (Cytotec)	When used alone – variable (~40-60%); used in combination with MTX or MFP efficacy is higher (Source - Micromedex)	NSAID-induced gastric ulcers	• Postpartum hemorrhage • Cervical ripening, labor induction • Pregnancy termination	"Cytotec should not be taken by pregnant women to reduce the risk of ulcers induced by NSAIDs "	"Cytotec administration to women who are pregnant can cause abortion … Cytotec should not be taken by pregnant women to reduce the risk of ulcers induced by NSAIDs… Patients must be advised of the abortifacient property and warned not to give the drug to others … "
Methotrexate (MTX)	When used alone – (IM injxn – variable); in combination with misoprostol efficacy is higher (80-90%; small Ns) (Source - Micromedex)	• Cancer • Psoriasis • Rheumatoid arthritis including juvenile	• Other Autoimmune diseases • More cancer • Pregnancy termination	"MTX can cause fetal death or teratogenic effects when administered to a pregnant woman MTX is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus Women of childbearing potential should not be started on MTX until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment "	"MTX has been reported to cause fetal death and/or congenital anomalies Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks Pregnant women with psoriasis or rheumatoid arthritis should not receive MTX "

*The off-label uses are general and based on tertiary sources; not on a formal drug use analysis.

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/s/

SUZANNE C BERKMAN ROBOTTOM
01/27/2012

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concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	February 17, 2012
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	202107 (cross reference IND 76480)
Applicant Name	Corcept Therapeutics, Inc.
Date of Submission	April 18, 2011
PDUFA Goal Date	February 17, 2012
Proprietary Name / Established (USAN) Name	Korlym (mifepristone immediate-release tablet)
Dosage Forms / Strength	300-mg tablets
Proposed Indication(s)	To control hyperglycemia in adult patients with endogenous Cushing's syndrome with T2DM or glucose intolerance who have failed surgery or are not candidates for surgery
Action/Recommended Action for NME:	Approval

1. Introduction

Corcept Therapeutics has submitted this new drug application (NDA) under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FDCA) for the use of Korlym® (mifepristone) in the treatment of patients with endogenous Cushing's syndrome who have failed surgery or are not candidates for surgery.

Cushing's syndrome is due to hypercortisolism and its clinical and metabolic consequences. It is broadly separated into exogenous and endogenous forms, the former due to exogenous glucocorticoid administration for varied medical conditions and the latter due to the body's over production of cortisol. Endogenous Cushing's syndrome is further divided into ACTH-dependent and ACTH-independent forms to distinguish between an extra-adrenal or intra-adrenal pathology.[1] As this application is only for the treatment of endogenous Cushing's syndrome, the remainder of this memo will refer to Cushing's syndrome with an understanding that it is specific to only the endogenous forms of this condition.

Approximately 80-85% of Cushing's syndrome are ACTH-dependent with 80% of these due to a pituitary tumor (Cushing's disease) and 20% due to ectopic ACTH secretion from a non-pituitary tumor with the most prevalent ones being bronchial carcinoid and small cell lung

[1] Pivonello R et al. Cushing's Syndrome. *Endocrinology and Metabolism Clinics of North America.* 2008; 37(1): 135-149.

cancer although any tumor of neuroendocrine origin may produce ACTH.[2] Of the approximate 15-20% of ACTH-independent Cushing's syndrome, the majority are due to an adrenal tumor. Cushing's syndrome is a rare disease with an incidence of 0.7 to 2.4 per million population per year. This application received orphan designation on July 5, 2007.

The diagnosis of Cushing's syndrome requires a multitude of laboratory and radiologic tests whose discussion extends beyond the scope of this memo. The objective of the laboratory tests is to demonstrate inappropriate and sustained hypercortisolism to distinguish these patients from conditions such as pseudo-Cushings, severe depression, or cyclical Cushing's. Reliance on just clinical presentations is not possible or acceptable as patients' presentations are highly variable and span a wide spectrum that includes textbook descriptions of buffalo hump, violaceous striae, hirsutism and facial plethora to more subtle signs of just diabetes and depression. The etiology of the syndrome may also influence the clinical presentation. For example, the age range of patients with ectopic ACTH syndromes is generally a decade older than those with Cushing's disease with a lower female to male ratio. Patients with ectopic ACTH syndrome or adrenal cancers may also present with more severe signs and symptoms of hypercortisolism, and due to the underlying malignant nature of the tumor, these patients often have greater morbidity.

Regardless of the etiology of Cushing's syndrome, the treatment goal is the same and in all cases, if the underlying tumor can be located, surgical resection is the preferred initial therapy. Medical therapy may be initiated prior to surgery to control the hypermetabolic state and is often relied upon afterwards if surgery is unsuccessful or the tumor recurs. In some patients, radiation therapy and/or bilateral adrenalectomy are considered. The available medical therapies are limited and unapproved for Cushing's syndrome.[3] Their use has been based on the knowledge of their effects at inhibiting certain enzymes in the adrenal steroidogenesis pathway (e.g., ketoconazole or metyrapone) or limited inhibition of ACTH (e.g., somatostatin). Mifepristone employs a different strategy in treating Cushing's syndrome: blockade of the glucocorticoid II receptor (GR) to inhibit the actions downstream from this receptor. It also blocks the progesterone and androgen receptor, the former activity being the basis for its use in termination of pregnancy.

2. Background

There were two main challenges in the review of this application. The first was a scientific matter and the second was a regulatory/legal one.

On the scientific note, the trial design to establish safety and effectiveness of Korlym for this indication was limited by 1) the underlying medical condition and 2) the pharmacologic action of the drug. Given the rarity and progressive nature of the condition with limited medical options, the type of trial design would have to be an uncontrolled and open-label design in a limited number of patients. Such a trial design in a small sample of patients complicates

[2] Alexandraki K and Grossman A. The ectopic ACTH syndrome. *Rev Endocr Metab Disord.* 2010; 11: 117-126.
[3] Mitotane is an exception but it has a limited indication in only patients with adrenal carcinomas

attribution of effect and safety to drug. The mechanism of action of the drug presented another complexity as to the appropriate endpoint to evaluate effectiveness of Korlym. Just as the diagnosis of Cushing's syndrome requires evidence of elevated cortisol levels, the treatment of these patients relies on a demonstration of reduced cortisol levels as a measure of response and/or success. Since the drug's selective antagonism of the GR does not result in reduced cortisol levels, this biomarker was not of any utility for establishing efficacy and could not be employed as a measure for dose titration. Sections 6.0 and 7.0 of my memo delve further into the trial design and how the reviewers considered multiple lines of evidence to make a determination of safety and effectiveness.

The regulatory and legal challenge of this application is because of the more controversial use of this active ingredient for medical termination of pregnancy in the approved formulation, Mifeprex®. Given as one-time lower doses than proposed in Cushing's syndrome, mifepristone binds to the progesterone receptor (PR) to achieve pregnancy termination. Mifeprex, manufactured by Danco, was approved on September 28, 2000 under 21 CFR Subpart H and is available only through a restricted distribution program. With passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) was applied to Mifeprex on June 8, 2011. Mifeprex is not distributed to or dispensed through retail pharmacies but is limited to specialty clinics and prescribed by physicians who have enrolled in a certification program. (Please see DRISK review for a full description of the Mifeprex REMS with ETASU).

Prior to the submission of Korlym and throughout the NDA review, multiple internal meetings and discussions were held to determine if Korlym and its proposed indication met the regulatory requirements for a REMS with ETASU or if one would be necessary to maintain the integrity of Mifeprex's REMS with ETASU.

Dr. Dragos Roman in his cross-disclipine team leader (CDTL) memo has clearly outlined these discussions and the reader is also referred to memos written by DRISK reviewers, Drs. Robottom, LaCivita, and Karwoski, and meeting minutes prepared by Dr. Amy Egan for a meeting involving CDER Center Director and senior managers in OND, OSE, and ORP. On November 3, 2011, a CDER recommendation was made that given the rarity and seriousness of Cushing's syndrome and the unique situation in which it would be used, a REMS with ETASU was not warranted. However, the applicant has agreed to establish a voluntary limited distribution system and a drug utilization study will be required postmarketing. Please see Section 13.0 for further discussions of the PMR for this application.

3. CMC/Device

CMC has recommended approval without any additional testing or studies required. Please see reviews of Drs. Ysern and Al-Hakim dated January 12, 2012.

4. Nonclinical Pharmacology/Toxicology

The applicant conducted several nonclinical studies to support the chronic use of mifepristone. These included safety pharmacology studies to evaluate potential of mifepristone to inhibit Ki channels, pharmacokinetic/ADME/and toxicokinetic studies, repeat-dose toxicity studies, in vitro genetic toxicology studies, and carcinogenicity studies. Published literature and studies conducted under approved NDA 20687 for use of mifepristone in pregnancy termination were also relied upon by the applicant as permitted under 505(b)(2). The three major metabolites of RU486 identified in humans were also present in mice, rats, dogs, and monkeys and were therefore adequately evaluated in the nonclinical program.

Please see Dr. Patricia Brundage's review dated January 19, 2012, for details of the nonclinical program supporting approval of this NDA. She and pharmacology/toxicology supervisor, Dr. Todd Bourcier, deem data acceptable in support of approval of mifepristone for Cushing's syndrome provided labeling accurately reflects the nonclinical findings and their recommendations on use of the product. Dr. Bourcier's memo dated February 7, 2012, also outlines the sufficient bridging data to Mifeprex® supporting reliance on FDA's finding of safety and effectiveness for some aspects of this application. No postmarketing trials are being proposed by this discipline.

Several of the safety findings identified reflect the pharmacology of mifepristone as an anti-glucocorticoid and anti-progesterogenic drug. The first of these effects is the basis for evaluating the use of mifepristone in the treatment of Cushing's syndrome. Antagonism at the progesterone receptor is also included in the label and discussed in other sections of this memo with regard to the effect on fertility and pregnancy.

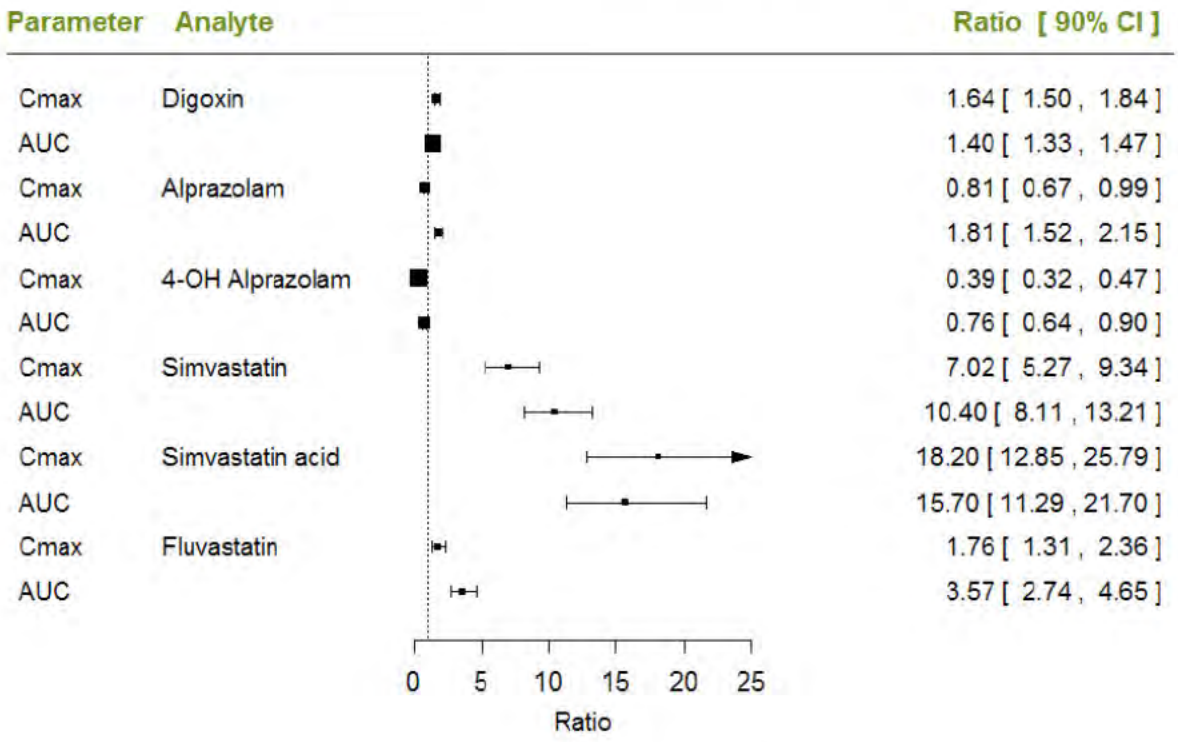
Two hERG channel studies were performed of which one showed a concentration-related inhibition of potassium selective IKr current with mifepristone and its metabolites. A 12-month toxicity study in dogs also revealed a slight QTc prolongation in higher-dosed animals. These findings alongside the clinical tQT study support information on the potential QT prolongation effect of mifepristone in labeling with caution to be applied when used with drugs which might increase mifepristone drug exposures.

5. Clinical Pharmacology/Biopharmaceutics

Please see review of Drs. Jee Eun Lee and Jayabharathi Vaidyanathn dated January 13, 2012. Thirteen clinical pharmacology studies have been conducted by applicant and submitted to this NDA.

Drug-drug interaction studies (DDI) were conducted with digoxin (P-gp substrate), alprazolam and simvastatin (CYP3A substrate), fluvastatin (insensitive CYP2C8/9 substrate), and cimetidine (mild CYP3A inhibitor). No DDI studies were conducted to address the effect of strong CYP3A4 inhibitors. The results from these studies are illustrated in the following figure:

Effects of Mifepristone on Other Drugs



*Simvastatin dose in multiple dosing regimen is 80 mg while 40 mg in single dosing regimen (Exposure was not normalized by dose)

Figure 10. Forest plot for DDI with mifepristone

Given the significant increase in sensitive CYP3A substrate simvastatin, contraindications are proposed for simvastatin and lovastatin plus other CYP3A4 substrate drugs with narrow therapeutic indices.

The applicant was asked to conduct a DDI with a potent CYP3A4 inhibitor. This was not done and the applicant instead provided 2 randomly-timed concentrations of mifepristone from one patient who was on concomitant ketoconazole therapy during his participation in Study 400. This was not deemed acceptable. (b) (4)

(b) (4)

(b) (4)

After further discussion it was decided that potential DDI with potent CYP3A4 inhibitors would be more appropriately discussed in Warnings and Precautions recommending against their use with mifepristone unless medically necessary. In addition the label will recommend limiting the dose of mifepristone to 300 mg daily if a strong CYP3A4 inhibitor must be used concomitantly. A DDI study with ketoconazole will be required. Depending on the results of this study, updates to labeling may occur.

Thorough QT Study

A tQT study was conducted; please see the IRT review dated October 20, 2011. This study was a 14-day, multiple-dose, parallel treatment design enrolling 180 healthy male subjects but due to adverse events resulting in high discontinuation rates, data are limited out to Day 14. Mifepristone doses of 600 and 1800 mg were employed, the latter providing supratherapeutic exposures. A single oral dose of moxifloxacin 400 mg was used as a positive control.

Overall, the study results were inconclusive because assay sensitivity was not established. The largest lower bound of the 2-sided 90% CI for the pbo-adjusted, baseline-corrected QTcI for moxifloxacin was < 5 ms; therefore, small changes in QTc interval cannot be excluded. Despite this shortcoming, the largest upper bounds of the 2-sided 90% CI for the mean difference between mifepristone 1800 mg and placebo did exceed 10 ms at several time points. No such finding was observed in the 600 mg dose group. This finding along with the one positive hERG channel study suggests a potential for QT prolongation associated with mifepristone use with increasing exposures.

The proposed label will note that mifepristone and its metabolites block IKr, based on nonclinical data, and that Korlym prolongs QTc interval in a dose-related manner. More cautionary language is proposed with regard to using lowest effective dose. Since a DDI study has not been conducted with a potent CYP3A4 inhibitor, we will recommend limiting dose of Korlym to 300 mg if combined use with a potent inhibitor is necessary. The applicant will be required to conduct this DDI study with ketoconazole. Depending on the results, labeling may be revised accordingly.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Limitations of Clinical Development Program to be Considered

One pivotal efficacy and safety trial was conducted by the applicant in support of this NDA. Published studies of mifepristone in Cushing's syndrome were also submitted and summarized in Dr. Zemskova's review but none of these studies was relied upon for the demonstration of efficacy of Korlym and are therefore not discussed in this memo.

C1073-400 or Study 400 was a 24-week, open-label, uncontrolled trial that enrolled a total of 50 patients with endogenous Cushing's Syndrome. The stated objectives of the trial were to evaluate the safety and efficacy of mifepristone in the treatment of the signs and symptoms of endogenous Cushing's syndrome. These are very broad objectives and in reality, only two endpoints were identified and patients were selected specifically to evaluate these endpoints: glycemic control and blood pressure.

Before presenting the trial results, a discussion on several aspects of the trial design, endpoints, and patient population, and how they impact data interpretability will be necessary.

Trial Design (Open-label and Uncontrolled)

The open-label and uncontrolled nature of a trial can introduce confounders, biases, and limitations that are often mitigated through the conduct of a randomized, double-blind, and controlled trial. For this condition, a placebo control arm could not be employed because the progressive and serious nature of the condition would make it unethical to randomize any patient to placebo.

An active-controlled trial to currently available therapies was not considered for several reasons. With exception for mitotane, which is approved for the treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types, all medical therapies employed in practice for the treatment of Cushing's syndrome are used off-label. The treatment regimens and efficacy of these other medical therapies have not been adequately assessed beyond case reports and anecdotal experience. In addition, these other drugs target a reduction in cortisol levels which cannot be achieved with Korlym by virtue of mifepristone's mechanism of action. Selecting an appropriate and easily quantifiable endpoint that can compare the effects of the off-label therapies and Korlym could not be identified for a well-designed, active-controlled trial. Similarly, radiotherapy, which is also a treatment option in Cushing's syndrome, would not be an appropriate active control given its variable success rate and time to demonstration of efficacy measured over the course of years.

Untreated hypercortisolism in Cushing's syndrome is progressive with little to no expectation of spontaneous improvement (e.g. the very rare instance of pituitary apoplexy in Cushing's disease). For this reason, an uncontrolled trial of Korlym that could assess a clinically relevant efficacy endpoint might produce results which can be reasonably attributed to the drug. However, this limitation of the trial design must still be considered in the evaluation and conclusions made of the study results.

Efficacy Endpoints

As stated in the Introduction and Background sections of this memo, the mechanism of action of Korlym is antagonism of the GR preventing the downstream effects of cortisol on its receptor. Unlike other interventions targeting a reduction in cortisol levels, Korlym does not reduce serum cortisol and in some cases cortisol levels may increase. Furthermore, despite biochemical hypercortisolism, patients can become adrenally insufficient as a result of absent post-receptor activation.

During the IND stage, FDA agreed with the applicant that demonstration of an effect on some other biochemical parameter will be accepted. The original protocol submission included very broad assessments of a composite clinical endpoint which was ultimately modified (with FDA input) to a demonstration on improvements in glycemic control and/or blood pressure defined as:

1. The change in the area under the concentration-time curve for glucose (AUCglu) in the 2-hr oral glucose tolerance test (oGTT) from baseline to Week 24
2. A change from baseline to Week 24 in mean diastolic blood pressure (DBP)

Secondary endpoints included a blinded assessment of selected signs and symptoms of Cushing's syndrome as well as laboratory findings by a Data Review Board, body weight, use of concomitant medications for diabetes and hypertension, levels of HbA1c, systolic blood pressure, and photographs. There were exploratory efficacy variables assessed which will not be discussed in this memo. It should be noted that no hierarchical sequence for analysis was applied in the analysis of secondary endpoints. Although FDA did not object to this, FDA did note that control of Type 1 error for secondary endpoints would be important for consideration of labeling.

The trial selected patients but did not randomize them into subgroups which would be evaluated specifically for one of the two primary endpoints. These subgroups are referred to as the Diabetes Mellitus (DM) and the Hypertension (HTN) cohorts.

FDA has well-established efficacy criteria for therapies intended for the treatment of hyperglycemia in diabetes mellitus. The primary efficacy endpoint in both T1 and T2DM trials has been HbA1c which is a reliable measure of glycemic control and a surrogate for clinical benefits (e.g., microvascular complications). HbA1c was not selected as a primary efficacy endpoint in the Cushing Syndrome population because the clinical presentation of diabetes is variable in this condition and adjustments in anti-diabetic therapies are expected which would hinder the interpretation of results, especially in an uncontrolled study. As the DM cohort also included a few patients with glucose intolerance, a change in HbA1c from baseline might not be as reliable of a measure in these patients as they would have normal values at baseline. Reliance on a change in AUCglu during a 2-hr oGTT is a reasonable alternative assessment of glycemic response as it is under a controlled setting (unlike self-blood-glucose monitoring); is administered via a protocol; and is an objective laboratory measure. Nonetheless, results can be influenced by certain patient behaviors. Furthermore, unlike HbA1c, the clinical relevance of a reduction in AUCglu during an oGTT is unknown. Hence, the effect of Korlym on glycemic control will focus on both this primary efficacy measure supported by changes in HbA1c and anti-diabetic medications.

Anti-hypertensive therapies have been approved based on mean changes in systolic and/or diastolic blood pressure. Hence, the endpoint of change in DBP is not unprecedented for drug approval. However, the effect of Korlym on blood pressure proved to be more difficult to demonstrate than anticipated and the results were obfuscated by the inclusion criteria, protocol violations, and use of certain anti-hypertensive medications. In retrospect, establishing efficacy of Korlym in Cushing's syndrome based on blood pressure reduction should not have

been considered a primary endpoint because the increased cortisol levels resulting from the drug's mechanism of action may actually exacerbate hypertension secondary to mineralocorticoid receptor activation. Nonetheless, this memo will highlight these results from both an efficacy and safety perspective.

Patient Population

Given the rarity of this condition, the sample size in the pivotal trial was only 50 which is a limitation for evaluating efficacy and safety for chronic use but not unexpected for orphan indications. FDA has approved other therapies for rare disease with similar sample sizes (NDA for Increlex included 71 pediatric patients with severe Primary IGF-1 deficiency).

It should be noted that despite the limited patient numbers in the pivotal trial, other clinical data of mifepristone in Cushing's patients from published literature served as supportive evidence for efficacy and informed us in the design of the Phase 3 trial. None of these studies, which are summarized under Section 6.1.10, 7.7.2, and 9.1 of Dr. Zemskova's review, will be included in labeling.

Efficacy in Diabetes (DM) Cohort

There were 29 out of 50 patients enrolled in Study 400 who were evaluated under the DM Cohort. Twenty-four (83%) had Cushing's disease; 3 had ectopic ACTH and 2 had adrenal carcinoma. Twelve of the 24 patients with Cushing's disease had prior radiation therapy whose data were reviewed separately by Dr. Zemskova to determine whether this previous treatment could account for any observed efficacy associated with Korlym. In her review, she pointed out that ACTH levels remained elevated in these patients despite radiation therapy. This would be evidence that radiation therapy was not successful and unlikely contributory to any efficacy observed in Study 400.

Patients in this cohort underwent a 75-g oGTT at screening, on Day 1, Wks 6, 10, 16, and 24 or on early termination visits. A patient was considered a responder if he/she had a 25% or more decrease in AUCglu at Wk 24 or early termination visit from baseline. A statistically significant reduction in AUCglu was defined by a responder analysis in which the lower bound of the 95% CI of this response rate had to exceed 20%. Approximately 60% of patients were responders and the lower bound of the 95% CI was 42%. From the cumulative distribution function curve provided by the applicant it is evident that the majority of patients had a reduction in AUCglu from baseline. The following table from Dr. Zemskova's review summarizes the individual response for the 24 patients included in this analysis.

Table 19. Cumulative Distribution Function for Percent Reduction in $AUC_{glucose}$ at Week 24/ET in C-DM Subjects (mITT population)

% Reduction from Baseline	Cumulative Distribution of Change, n (%)	Improved/ Worsened
-68.7	1 (4.17)	Improved
-60.6	2 (8.33)	Improved
-50.7	3 (12.50)	Improved
-48.2	4 (16.67)	Improved
-47.0	5 (20.83)	Improved
-46.5	6 (25.00)	Improved
-45.3	7 (29.17)	Improved
-43.9	8 (33.33)	Improved
-42.4	9 (37.50)	Improved
-41.2	10 (41.67)	Improved
-37.1	11 (45.83)	Improved
-36.9	12 (50.00)	Improved
-35.3	13 (54.17)	Improved
-28.0	14 (58.33)	Improved
-25.0	15 (62.50)	Improved
-24.2	16 (66.67)	Improved
-19.8	17 (70.83)	Improved
-4.4	18 (75.00)	Improved
-3.8	19 (79.17)	Improved
-3.5	20 (83.33)	Improved
-0.8	21 (87.50)	Improved
4.7	22 (91.67)	Worsened
26.5	23 (95.83)	Worsened
33.2	24^ (100.00)	Worsened

Source: Sponsor's table 15, Module 5, Vol 31, p. 73;
^One subject was excluded from mITT analysis (#20-022), because he did not have $AUC_{glucose}$ values post-baseline.

In those patients who responded to treatment, a reduction in AUCglu was observed by Week 6 in most patients and was sustained for the duration of treatment out to Week 24 (see Figure 3 in Dr. Zemskova's review).

As stated above, AUCglu is not a standard efficacy endpoint for anti-diabetic medications and was accepted only for the unusual circumstances of evaluating glycemic control in Cushing's patients treated with Korlym. However, the applicant also provided data on HbA1c reduction in 21 patients who had baseline and post-baseline values. The mean reduction from baseline in these patients was 1.14% (2-sided 95% CI: -1.56, -0.65; p=0.0001). This magnitude of reduction has been observed in currently approved anti-diabetic applications and considered to be clinically relevant. Dr. Zemskova further evaluated those patients with HbA1c levels above normal at baseline (6.5% - recall that trial enrolled patients with glucose intolerance or could have enrolled a diabetic patient with adequate control). In 14 patients with elevated HbA1c levels at baseline, all had a reduction from baseline including some with robust reductions of 2 to 4% accompanied by reductions in anti-diabetic medications or doses.

In conclusion, while this trial employed an untraditional measure of glycemic control and was uncontrolled, a correlation of AUCglu to clinically meaningful endpoints such as HbA1c reduction and dose reduction of antidiabetic medications could be established including several very robust effects (e.g., reduction from 10.4 to 6.0% in HbA1c level in one patient or

~ 50% reduction in insulin requirements). These data constituted substantial evidence that Korlym would treat hyperglycemia associated with diabetes or glucose intolerance in Cushing's syndrome. However, the observed effects should not be extrapolated beyond this patient population and it would be inappropriate to consider the use of Korlym in the management of diabetes unrelated to hypercortisolism due to Cushing's syndrome. Labeling should indicate this as a Limitation of Use.

Efficacy in Hypertension (HTN) Cohort
Unlike the effect observed in the DM-cohort, the response rate in the HTN cohort was equivocal. Drs. Zemskova and Roman discuss some of the design flaws which might have contributed to the difficulty in establishing a robust effect and I will not reiterate them here. I believe that some aspect of the results reflect the pharmacologic effect of mifepristone. Hypertension in Cushing's syndrome is partly due to high circulating levels of cortisol which can bind to the mineralocorticoid receptor. Acting like aldosterone, patients can present with hypokalemia and hypertension. Since mifepristone blocks the glucocorticoid receptor but does not cause a reduction in circulating cortisol levels, these patients are still prone to mineralocorticoid effects of hypercortisolism.

Effects on Clinical Signs and Symptoms of Cushing's Syndrome in Overall Cohort
It should be noted that no plan was submitted to FDA for review by the Study Endpoints and Labeling of Drugs (SEALD) review team with respect to patient reported outcome measures. FDA reviewers have determined that while these endpoints should be evaluated in a clinical trial, the limitations of the assessments in an open-label, uncontrolled trial should preclude any quantitative statements in labeling.

A Data Review Board (DRB) comprised of 3 experts on Cushing's syndrome performed a review of 8 categories of clinical parameters to evaluate whether a patient's signs and symptoms of Cushing's had changed. These categories included:

1. assessment of glucose homeostasis
2. assessment of blood pressure
3. assessment of lipids
4. changes in weight and body composition
5. clinical scoring and appearance (e.g., acne, hirsutism (in women only), Cushingoid appearance)
6. strength assessments
7. psychiatric and quality of life assessments
8. metabolic bone assessments

The DRB reviewed adverse events, concomitant medication data, and all efficacy assessments obtained at baseline, Weeks 6, 10, 16 and 24 or end of treatment, and at the follow-up visit. Baseline and follow-up evaluations were identified, but data from other visits were reviewed in a blinded fashion with respect to visit. The DRB did not know the dose of drug or the sequence in which the visit occurred. It should be noted that while the DRB reviewers are blinded to the sequence of visits, some of the assessments at each visit were evaluated by a

clinical investigator who was NOT blinded. After reviewing the data, each DRB member assigned an overall score for each visit as follows:

-1: worse than baseline
0: unchanged from baseline
+1: clinically significant improvement

The median of the 3 scores was calculated and a score of +1 was considered evidence of clinical improvement. A responder was defined as a subject whose median score was +1 at any visit after the baseline visit. Based on the applicant's definition of responders, they report that 87% of patients (40/46) in the mITT population had a clinical improvement at any point in time and deemed the findings statistically significant based on a calculated 95% CI yielding a lower bound of > 30%, an arbitrary cut point considered by applicant as adequate to account for variability in response.

Drs. Zemskova and Choudury appropriately point out the limitations of this endpoint assessment. The open-label nature of the trial is always problematic in evaluating subjective measures such as quality of life where patient reports may be perceptions based on expectations of clinical improvements or side effects based on knowledge that he/she is receiving an investigational agent. This is further compounded by the absence of a control group for comparison of response for the less subjective measures. In addition, declaring a patient as a responder at any visit also allows the applicant many opportunities for concluding success on this endpoint.

Finally, it is not clear how the reviewers ranked the clinical relevance of the 8 clinical parameters in their scoring. The form for this scoring is provided below.

Corcept

Data Review Board Evaluation

Corcept Therapeutics

Study: C1073-400

BLINDED REVIEW RESULTS				
Subject ID: _____				
REVIEWER NAME: _____ *Printed Name*				
Scoring: -1 = Worse than Baseline 0 = Unchanged from Baseline +1 = Clinically significant improvement from Baseline				
VISIT	**RESULT** *(Please check one (and only one) box per visit)*			
VISIT A	☐ -1	☐ 0	☐ +1	☐ N/A- No data
VISIT B	☐ -1	☐ 0	☐ +1	☐ N/A- No data
VISIT C	☐ -1	☐ 0	☐ +1	☐ N/A- No data
VISIT D	☐ -1	☐ 0	☐ +1	☐ N/A- No data

Reviewer Signature:	
Review Date:	__ __ *day* __ __ __ *month* __ __ __ __ *year*

There is no breakdown of how response in categories such as blood pressure or metabolic parameters might have contributed to the scores or if there was worsening in one and improvement in another, how these components were weighted in the overall score of -1, 0 or 1. To add further to the subjectivity of this assessment, it is not clear how some of these parameters which had their own scoring system were translated to the -1, 0, or 1 categories. For example, acne was rated using a Global Acne Scoring System (CAGS) by the clinical investigator not the DRB reviewer which is described under Section 18.3.3.1 of the applicant's Clinical Study Report. Different locations of the body are assessed and given a Grade of 0-4 which contributed to a Local Score. The sum of the Local Scores is called the Global Score for acne and can be: 0 None; 1-18 Mild; 19-30 Moderate; 31-38 Moderately Severe; or > 39 Severe. Did a Global Score of 40 on one visit and 38 on another get rated as 0 or +1 by the blinded DRB reviewer?

Despite the inability to rely on these assessments, review of patient narratives does point to individual responses on some endpoints. Care for these patients by several on the FDA review team has given us an appreciation that for many of these patients who have limited options, some of these clinical responses are meaningful, even if other signs or symptoms show worsening. While the label will not state that Korlym is indicated for improving clinical signs and symptoms of Cushing's syndrome, a statement under the Clinical Studies section describing the variable responses to treatment, including some patients reporting improvement, was considered appropriate by the review team provided that no statistical significance be applied to any of these findings.

8. Safety

In contrast to the review of efficacy which relied on one trial, safety of Korlym was based on Study 400, its ongoing extension (Study 415), and several Phase 1 , 2 and 3 studies, including studies conducted by the applicant using Korlym for the treatment of other medical conditions. For purposes of labeling, only some of these studies were relied upon. Please see Dr. Zemskova's review for a thorough assessment of safety based on all studies submitted or referenced. Given the variable patient population and study designs, safety data across studies were not pooled.

Just as it was the case in evaluating efficacy, the absence of a control group in Study 400 and 415 is a limitation in assessing a causal relation to drug treatment in the assessment of safety. Furthermore, the co-morbidities associated with Cushing's syndrome often result in serious complications. This is evident in Dr. Zemskova's review of several nonfatal serious adverse events in which she ascribed certain events to drug or as being exacerbated by drug only after careful consideration of the clinical presentation. Despite the lack of a control group, adverse events related to the mechanism of action of mifepristone should be anticipated. Please see section 7.3.5 of Dr. Zemskova's review and Dr. Roman's CDTL memo for a discussion of events of adrenal insufficiency, endometrial hyperplasia/vaginal bleeding and mineralocorticoid excess resulting in severe hypokalemia. Specific sections under Contraindications and Warnings and Precautions will convey these safety concerns.

There were 5 deaths in Studies 400 and 415: four occurred during Study 400 and one during Study 415. The narratives for these deaths are summarized in Section 7.3 of Dr. Zemskova's review who considered the deaths related to progression of disease. Three patients who died in Study 400 had metastatic adrenal carcinoma and the 4th patient had ectopic ACTH-secreting neuroendocrine carcinoma with metastases. The 5th patient in Study 415 had Cushing's disease. The patient was noted to have markedly elevated alkaline phosphatase and bilirubin at the onset of Study 415. Further work-up included a liver biopsy revealing amyloidosis, and a bone marrow aspirate revealing multiple myeloma. The patient's condition deteriorated rapidly thereafter with development of renal failure, hypotension and disseminated intravascular coagulation prior to death.

As noted in the Introduction, mifepristone's antagonism of the progesterone receptor is used in combination with misoprostol for medical termination of pregnancy. The higher doses of mifepristone used in the treatment of Cushing's syndrome are expected to have a similar effect in a pregnant woman. However, differences in this patient population lend themselves to a lower likelihood of unplanned pregnancy and termination. The hypercortisolemic state often renders a patient amenorrheic from secondary hypogonadism. Furthermore, the high doses of mifepristone used for glucocorticoid antagonism is also a contraceptive. Nevertheless, all female patients had to have negative pregnancy screening prior to initiation of therapy and women of childbearing potential had to use an acceptable non-hormonal form of contraception with regular counseling against becoming pregnant. No pregnancies were reported in this program.

Other safety concerns which will be discussed in labeling include immunosuppression, increased TSH levels and rash. Of note, immunosuppression should be discussed with the following in mind:

Immunosuppression – predisposition to infections
Patients with Cushing's syndrome are immunocompromised due to the hypercortisolemic state. In addition, these patients have other co-morbidities (e.g., diabetes) which increase the risk of infections in this patient population. Several infections were reported by Dr. Zemskova but one should be discussed only as it has been reported in the literature as related to the effective control of hypercortisolemia.

A 41 yo male with ectopic Cushing's syndrome secondary to metastatic thymic carcinoid was diagnosed with pneumonia about one month after initiation of Korlym. The patient was treated for presumed Pneumocystis jirovecii (formerly carinii). This case is described on page 118 of the clinical review.

Pneumocystis jirovecii is known to occur in severely immunocompromised patients and several reports of this form of pneumonia occurring in Cushing's syndrome have been reported in published literature.[4,5,6] In some reports, the pneumonia was diagnosed shortly after treatment for Cushing's was initiated. The authors of these reports suspect a subclinical picture of pneumocystis in patients with Cushing's syndrome due to their immunocompromised state which is kept at bay by high circulating cortisol levels. With a reduction in cortisol levels or a blockade of cortisol activity, this suppression of an acute immune response to the infection is disrupted resulting in severe pulmonary distress and compromise. Supporting this notion is the recognition in the 1990s that addition of high dose glucocorticoids to antibiotic treatment of pneumocystis in AIDS patients resulted in improved clinical outcomes.

[4] Arlt A et al. Fatal pneumocystis jirovecii pneumonia in a case of ectopic cushing's syndrome due to neuroendocrine carcinoma of the kidney. *Exp Clin Endocrinol Diabetes*. 2008 Oct; 116(9):515-9.
[5] Oosterhuis JK et al. Life-threatening pneumocystis jiroveci pneumonia following treatment of severe Cushing's syndrome. *Neth J Med*. 2007 Jun;65(6):215-7.
[6] Kim DS et al. Pneumocystis carinii pneumonia associated with a rapid reduction of cortisol level in a patient with ectopic ACTH syndrome treated by octreotide and ketoconazole. *Exp Clin Endocrinol Diabetes*. 2001;108(2):146-50.

Immunosuppresion – treatment with exogenous glucocorticoids
Dr. Zemskova described six adverse events related to exacerbation of an autoimmune disorder. This may be treatment-related in that mifepristone will block the immunosuppressive effects from exogenous steroid use. (b) (4) during negotiations, the label was modified to contraindicate the use of Korlym in serious medical conditions in which steroids would be required (e.g., post-organ transplant). There may be certain medical conditions in which Korlym dose may be reduced or held for short courses of glucocorticoid therapy.

Other concerns of hypercortisolemia
The clinical and metabolic effects of Cushing's syndrome results for elevated cortisol levels which is not eliminated with Korlym. The effects of cortisol extend beyond that of glucose metabolism and include, but are not limited to, wound healing, bone differentiation and metabolism, lipid metabolism, and mineralocorticoid effects. These concerns could not be adequately assessed in this program given the trial design and size of the patient population but one effect of hypercortisolemia that was apparent in this program can be attributed to the binding of cortisol to the mineralocorticoid receptor. This effect was manifested as hypokalemia although the increased blood pressure might also be a consequence of hypercortisolemia although there was poor correlation of cortisol levels with HTN in this program. Another potential effect of cortisol on the mineralocorticoid receptor would relate to effects on myocardial tissues as the mineralocorticoid receptor is also expressed in cardiac myocytes and its activation has been associated with tissue damage in heart failure and post-MI patients.[7] One patient in Study 400 developed worsening cardiomyopathy during treatment and had another episode after drug discontinuation. One other patient in Study 415 had developed mild heart failure responsive to diuretic therapy. Again, a causal association can not be established based on these two reports in this uncontrolled clinical trial. It should also be noted that improvement in heart failure was reported with mifepristone in the published literature and summarized in Dr. Zemskova's review.[8] However, published literature also supports the potential role of glucocorticoid and RU486 on expansion of infarct area in rodent studies that is ameliorated by spironolactone.[9] Although this clinical development can not provide any adequate CV risk assessment of Korlym or hypercortisolemia, it would be appropriate to include under the Warnings and Precautions section to use caution in patients with underlying heart disease including heart failure.

9. Advisory Committee Meeting

Korlym is not a new molecular entity requiring discussion before an advisory committee. However, it was acknowledged early in the review process that if approved, this would be a novel medical therapy for Cushing's syndrome and there may be concerns about expanded availability of mifepristone which is currently only available as Mifeprex under a restricted distribution program for medical termination of early term pregnancy.

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[7] Funder JW. Reconsidering the roles of the mineralocorticoid receptor. *Hypertension*. 2009; 53: 286-290.
[8] Chu et al. Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone. *J Clin Endocrinol Metab*. 2001; 86:3568-3573.
[9] Mihailidou et al. Glucocorticoids activate cardiac mineralocorticoid receptors during experimental myocardial infarction. *Hypertension*. 2009; 54:1306-1312.

An advisory committee was not considered necessary to discuss the clinical development program as it was felt that the scope of the program for an orphan disease was not out of the ordinary. The selected efficacy endpoints were clinically relevant to the disease and scientifically sound based on the drug's mechanism of action. Similarly, the safety concerns predicted with the drug were also based on knowledge of the pharmacologic action. Review of the clinical studies did not yield any different conclusion.

The need for a restricted drug distribution plan is discussed under Section 13.

10. Pediatrics

Korlym was granted orphan drug status. Pediatric studies are therefore waived under PREA.

11. Other Relevant Regulatory Issues

(b) (4)

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(b) (4). FDA has already negotiated a more limited patient population with Korlym than was originally proposed by the applicant. The fact that cortisol levels cannot be relied on for the monitoring of clinical response and drug toxicity was known during the IND stage (b) (4). Given the limited availability of medical therapies, which themselves are used off-label with their own toxicities, I still conclude that with careful monitoring and cautious titration of Korlym by physicians experienced in the care of patients with Cushing's syndrome, a reasonable balance of benefit to risk can be achieved.

12. Labeling

One of the objectives of the prescriber and patient labeling is to convey that Korlym will cause pregnancy termination and that it is NOT to be used in a pregnant patient. To achieve this, multiple sections of labeling reiterate this as summarized below:

Prescriber labeling will include a BOXED WARNING

WARNING: TERMINATION OF PREGNANCY

See full prescribing information for complete boxed warning.

Mifepristone has potent antiprogestational effects and will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with Korlym.

Under CONTRAINDICATIONS Section 4.1 the label will state:

4.1 Pregnancy

Korlym is contraindicated in women who are pregnant. Pregnancy must be excluded before the initiation of treatment with Korlym. Nonhormonal contraceptives should be used during and one month after stopping treatment in all women of childbearing potential. *[See Use in Specific Populations 8.8]*

Under USE IN SPECIFIC POPULATIONS 8.1 Pregnancy:

8.1 Pregnancy

Category X

Korlym is contraindicated in pregnancy. Korlym can cause fetal harm when administered to a pregnant woman because the use of Korlym results in pregnancy loss. The inhibition of both endogenous and exogenous progesterone by mifepristone at the progesterone-receptor results in pregnancy loss. If Korlym is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. *[See Contraindications (4.1)]*

Under PATIENT COUNSELING INFORMATION

17.1 Importance of Preventing Pregnancy

- Advise patients that Korlym will cause termination of pregnancy. Korlym is contraindicated in pregnant women.
- Counsel females of reproductive potential regarding pregnancy prevention and planning with a non-hormonal contraceptive prior to use of Korlym and up to one month after the end of treatment.
- Instruct patients to contact their physician immediately if they suspect or confirm they are pregnant.

And the first item in the Medication Guide, What is the most important information I should know about Korlym is:

Korlym can cause serious side effects.

1. **Loss of a pregnancy**

   For women who can become pregnant, you must:

   - Have a negative pregnancy test:
     - before starting Korlym
     - before restarting Korlym if you stop taking it for more than 14 days
   - Use a non-hormonal form of birth control during treatment with Korlym and for 1 month after stopping treatment. Talk to your doctor to find out how to prevent pregnancy. Tell your doctor right away if you think you may be pregnant.

FDA has also limited the indication to the smaller subset of patients with Cushing's syndrome as follows:

Korlym (mifepristone) is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have diabetes mellitus type 2 or glucose intolerance and have failed surgery or are not candidates for surgery.

Please see the approved label accompanying the action letter as there are many other important risks and benefit information conveyed beyond pregnancy termination.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

When prescribed to the selected population of Cushing's syndrome who have diabetes or glucose intolerance AND have failed surgery or are not candidates for surgery, a benefit of Korlym therapy can be ascribed to the observed improvements in glucose control. In addition to a reduction in AUCglu after an oral glucose challenge, a reduction in HbA1c was also observed and several patients had reductions in anti-diabetic medication requirements. The long-term benefits of glucose control in this population are not known but expectation of such a demonstration for this indication is neither feasible nor reasonable given that the population indicated is circumscribed to those who have limited options. In most patients, the shortened life expectancy makes the concern of long-term benefits of glycemic control less paramount.

Korlym is not without risks, some being very serious due to the mechanism of action of the drug. Given that these risks are predictable, appropriate labeling and use of Korlym by specialists well-versed in the care of patients with Cushing's syndrome should allow safe and effective use for the indicated population.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The serious safety concerns associated with Korlym use for the treatment of adults with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance include adrenal insufficiency, hypokalemia, vaginal bleeding, potential for QT prolongation, and drug-drug interactions. These safety concerns and others identified in the product label can be managed effectively through prescriber labeling and a Medication Guide.

The safety concern in a pregnant woman is termination of her pregnancy. The likelihood that patients in the intended population will fall into this category is low. The hypercortisolemic state of these patients often results in amenorrhea and infertility through secondary hypogonadism. Chronic therapy of mifepristone at the doses necessary to control hypercortisolemia is also an effective contraceptive. For both these reasons, the probability that a Cushing's patient will become pregnant while on Korlym is very low. Regardless, the label will include a boxed warning and a contraindication for its use in pregnant women (Please see section 12 of memo). A contraindication is the most stringent safety warning in an FDA-approved labeling as under 21 CFR 201.57 it means that the risk from use of Korlym clearly outweighs any possible therapeutic benefit in the pregnant patient. The label will also recommend use of a nonhormonal contraceptive in women of childbearing potential during and for at least one month after stopping treatment with Korlym.

The concern that Korlym may be used intentionally by women seeking an abortion (off-label use) was also considered in the approval of this application and whether it would require a REMS with ETASU (restricted distribution) to prevent off-label use. Given that the safety concerns associated with Korlym in its intended population does not support a REMS with ETASU and that the patients are severely ill with limited options, it was determined that establishing a REMS with ETASU to prevent off-label use established an unnecessary hurdle for a patient population with a serious and life-threatening disease.

With the NDA submission, the applicant proposed to establish a distribution program through a central pharmacy under the Support Program for Access and Reimbursement for Korlym (SPARK). Physicians can submit their prescriptions through this central pharmacy to have Korlym delivered directly to the patient. Distribution through a central pharmacy not only ensures timely access to treatment because it is unlikely that many pharmacies will keep Korlym stocked for the few patients eligible for treatment (~5000) but it will also limit its availability for potential off-label use.

- Recommendation for other Postmarketing Requirements and Commitments

The applicant will have two PMRs:

1. conduct a DDI study between ketoconazole and mifepristone to characterize the effect of a potent CYP3A4 inhibitor on mifepristone exposures.
2. conduct a drug utilization study to better characterize reporting rates for adverse events of interest associated with chronic Korlym use.

The drug utilization study will provide a denominator for adverse events reported with the use of Korlym, thus allowing an estimate of reporting rates which can be assessed in the context of the known background incidence rates of these adverse events in the Cushing's population. The reports of these adverse events of interest (endometrial hyperplasia and/or vaginal bleeding, retinopathy, and major adverse cardiovascular events) will be gathered through enhanced pharmacovigilance (15-day expedited reporting). Additional information such as gender and age of patient, dose and duration of use, and prescriber specialty can also be obtained through the drug utilization study which will provide some insight on whether the population prescribed Korlym reflects the indicated use of the product. But in addition to the measures established to ensure access to Korlym to patients with Cushing's syndrome who have limited options, FDA will need to communicate to the public that this drug is contraindicated in pregnant patients. Those seeking to use the same active ingredient for pregnancy termination must obtain it through a different program designated by FDA to ensure the safe and effective use of Mifeprex for early medical termination of pregnancy.

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/s/

MARY H PARKS
02/17/2012

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]
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	[redacted]
	[redacted]
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Review Completion Date	December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

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EXECUTIVE SUMMARY

This review provides the [redacted] rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the "in-person dispensing requirement" for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[a] This review provides the analysis of the (b) (6) ((b) (6) and the (b) (6) ((b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

[a] Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

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

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

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

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.

- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.

- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.

- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.[c]

- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.

- 1/12/2021: US Supreme Court granted a stay of that injunction.

- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

[c] *See* Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form.* FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.

- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.

- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.

- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.

- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.[d]

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- (b) (4) .
- 11/02/2021: A (b) (6) ((b) (6) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The (b) (6) (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

[d] Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.

- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.

- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.

- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)

- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.

- Publications that provided only general statistics on abortion care in the United States.

- Information pertinent to molecular or other basic science aspects of mifepristone.

- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.

- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

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

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

pregnancy, to diagnose an ectopic pregnancy,[e] and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

[e] American College of Obstetricians and Gynecologists (ACOG) Practice Bulleting Number 191, February 2018. Tubal Ectopic Pregnancy. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[f]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6) ((b) (6)), along with the (b) (6) ((b) (6)), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 review[g] is summarized here as follows:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and documentation of informed consent and evidence shows that practitioners are providing appropriate patient

[f] REMS@FDA, https://www.accessdata fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.
[g] (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af803dc7bd&_afrRedirect=386175573203745

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the (b) (6) March 29, 2016 review and a memorandum from the signatory authority in (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.[h,i]

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies[1,2] (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong[3], Kerestes[4]). Aiken[5] reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca[6] described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

h (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.
i (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe[7]) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent "witnessed by the counselor". Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient's informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation's 2020 Clinical Policy Guidelines for Abortion Care[8] continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG[9] and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017[10] of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman[11] conducted a US survey in

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/ gynecologists by Daniel in 2021[12] evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% −112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% −207%) and the South (+ 118%, 95% CI: 103% −134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)[j] REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.[13] The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

[j] This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the *ACOG* case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.[k,l]

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.[m,n] (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of (b) (4)

[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 [(b) (4)] 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).

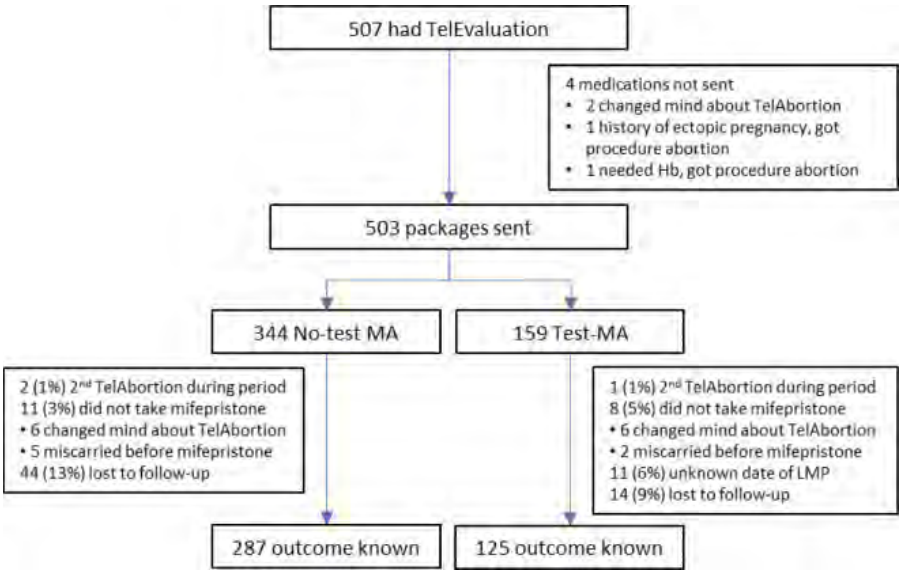
Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider 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

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) (4) 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) (4) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

[aa] Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

6. References

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7. Appendix A

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References cited in letter from *Chelius v. Becerra* Plaintiffs (September 29, 2021)	
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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)
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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.

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References included in the REMS review
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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.
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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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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.

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

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 Name(s): _____

Practice Setting Address: _____

_____

Email: _____ Phone: _____ Preferred __ email __ phone

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 03/2023

Induced Abortion Provision Among a National Sample of Obstetrician–Gynecologists

Daniel Grossman, MD, Kate Grindlay, MSPH, Anna L. Altshuler, MD, MPH, and Jay Schulkin, PhD

OBJECTIVE: To estimate the proportion of obstetrician–gynecologists (ob-gyns) who provided induced abortion in the prior year, disaggregated by surgical and medication methods, and document barriers to provision of medication abortion.

METHODS: In 2016–2017, we conducted a cross-sectional survey of a national sample of American College of Obstetricians and Gynecologists Fellows and Junior Fellows who were part of the Collaborative Ambulatory Research Network. We sent the survey by email, and mailed nonresponders paper surveys. We performed descriptive statistics, χ^2 tests, and logistic regression analyses.

RESULTS: Sixty-seven percent (655/980) of Collaborative Ambulatory Research Network members responded. Ninety-nine percent reported seeing patients of reproductive age, and 72% reported having a patient in the prior year who needed or wanted an abortion. Among those seeing patients of reproductive age, 23.8% (95% CI 20.5%–27.4%) reported performing an induced abortion in the prior year; 10.4% provided surgical and medication abortion, 9.4% surgical only, and 4.0% medication only. In multivariable analysis, physicians practicing in the Midwest (adjusted odds ratio [AOR] 0.31, 95% CI 0.16–0.60) or South (AOR 0.22, 95% CI 0.11–0.42) had lower odds of provision compared with those practicing in the Northeast, whereas those practicing in an urban inner city (AOR 2.71, 95% CI 1.31–5.60) or urban non–inner-city area (AOR 2.89, 95% CI 1.48–5.64 vs midsize towns, rural areas, or military settings) had higher odds of provision. The most common reasons for not providing medication abortion were personal beliefs (34%) and practice restrictions (19%). Among those not providing medication abortion, 28% said they would if they could write a prescription for mifepristone.

CONCLUSION: Compared with the previous national survey in 2008–2009, abortion provision may be increasing among practicing ob-gyns, although important geographic disparities persist. Few provide medication abortion, but uptake might increase if mifepristone could be prescribed.

(Obstet Gynecol 2019;133:477–83)
DOI: 10.1097/AOG.0000000000003110

In a 2018 analysis of induced abortion care in the United States, the National Academies of Sciences, Engineering, and Medicine concluded that legal induced abortion is safe and effective, yet the quality of care varies geographically owing to state-level regulations.[1] Timeliness and equity, two dimensions of quality, greatly depend on the distribution of services, requiring care to be readily available locally to all women when needed. Obstetrician–gynecologists

From Advancing New Standards in Reproductive Health (ANSIRH), Bixby Center for Global Reproductive Health, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, Oakland, California; Ibis Reproductive Health, Cambridge, Massachusetts; California Pacific Medical Center, San Francisco, California; the University of Washington, Seattle, Washington; and the American College of Obstetricians and Gynecologists, Washington, DC.

Supported by the Society of Family Planning Research Fund (SFPRF). The views and opinions expressed are those of the authors and do not necessarily represent the views and opinions of SFPRF. Additional support was provided by the Maternal and Child Health Bureau (Title V, Social Security Act, Health Resources and Services Administration, and Department of Health and Human Services), Grant UA6MC19010. The funding sources had no role in the study design; the collection, analysis, and interpretation of the data; nor the preparation, writing, or submission of this manuscript.

Presented as a poster at the North American Forum on Family Planning, October 14–16, 2017, Atlanta, Georgia.

The authors thank Neko M. Castleberry and Lauren M. Stark for their assistance with data collection and cleaning.

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

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Financial Disclosure
The authors did not report any potential conflicts of interest.

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(ob-gyns) play an important role in ensuring timely access to abortion care because they may be the first clinicians a patient with an unintended pregnancy encounters.

The most recent representative survey of U.S. ob-gyns performed in 2008–2009 found that 14% reported providing abortion care.[2] Female physicians and physicians living in an urban area or reporting they were Jewish were significantly more likely to provide abortions, whereas those older than 35 years of age, living in the South and Midwest (compared with the Northeast), or reporting high religious motivation were less likely to provide. The survey did not ask about the abortion methods provided. Medication abortion has become increasingly popular in recent years, accounting for 31% of nonhospital abortions in 2014.[3] However, a study from 2007 suggested that uptake of medication abortion among those not already providing surgical abortion was limited.[4]

The objective of this study was to provide an updated estimate of the proportion of ob-gyns who provide induced abortion, disaggregated by method, as well as physician and practice characteristics associated with provision. We also aimed to explore the barriers to provision of medication abortion, including the requirement to stock mifepristone in one's office.

METHODS

This cross-sectional survey included Fellows and Junior Fellows of the American College of Obstetricians and Gynecologists (ACOG) who were currently in practice. The American College of Obstetricians and Gynecologists is a professional society that represents approximately 90% of practicing U.S. ob-gyns and has more than 58,000 members. The study population included 1,000 members of ACOG's Collaborative Ambulatory Research Network, which is a demographically representative group of practicing ACOG members who voluntarily participate in surveys conducted by the ACOG Research Department.[5] We randomly selected 1,000 participants from a list of more than 1,400 current members of the Collaborative Ambulatory Research Network. With a minimum response rate of 60%, the maximum margin of error in the estimation of proportions with a 95% CI in a random sample of 600 participants is $\pm 4.0\%$.

Data collection took place between August 2016 and March 2017. We initially invited participants via email with a link to access the survey, which was administered using Qualtrics software. The email invited participants to complete a survey on "selected ob-gyn practices" and said the survey included "questions about how you manage patients with early pregnancy loss and unintended pregnancy and those seeking contraception." Those who were retired or did not wish to participate were given a link to opt out. We sent email reminders weekly for 5 weeks to those who had not completed the survey, and we mailed one postcard reminder. Participants who had not completed the electronic survey after these reminders were mailed a paper version of the questionnaire and a prepaid return envelope. We sent a second mailing containing a shortened version of the questionnaire to those who completed neither the electronic nor the first mailed survey.

We pretested the survey among practicing ob-gyns for meaning and respondent interest. The final version included 14 demographic questions and 19 questions about induced abortion provision (the shortened version contained eight abortion questions), in addition to questions on other family planning topics. Participants who reported that at least some of their patients were of reproductive age (15–49 years old) were asked whether they "had any patients in the last 12 months who wanted or needed an abortion or termination of pregnancy." If they answered affirmatively, we then asked whether, in the prior 12 months, they had provided a surgical abortion (dilation and sharp curettage, electric or manual vacuum aspiration) or a medical (medication) abortion. If they did provide any abortion care, we asked them to estimate the number of procedures and the locations where the procedures took place (ambulatory surgical center, hospital operating room, outpatient office setting of primary practice, Planned Parenthood or other specialized clinic, or other location).

Because medication abortion may be easier to provide in one's office than surgical abortion, we specifically explored the barriers to providing the former. We asked those who did not provide medication abortion in the prior year their reason. Participants could select from a list of 10 responses or write in a response, and multiple responses were allowed.

The U.S. Food and Drug Administration requires Mifeprex (mifepristone 200 mg) to be dispensed by the clinician in an office, clinic, or hospital; it may not be dispensed by prescription at a pharmacy.[6] To determine whether this is a barrier to provision, we asked participants who reported not providing medication abortion the following: "Currently, if you want to provide medical abortion, you must stock the medications in your office. Would you offer medical abortion to your patients if you could write a prescription for mifepristone and misoprostol, and your patient

could obtain both medications at a pharmacy?" Participants could select yes, no, or not sure.

To ensure data entry accuracy, 5% of all mailed questionnaires were randomly selected for review. We found only one consistent data entry error (a coding error on the shortened paper surveys), prompting all shortened surveys to be reviewed.

We conducted data analyses with Stata 15.1. Respondents who answered the primary outcome questions on whether they provided medication or surgical abortion in the past 12 months were included in the analysis. Responses that were incorrectly given (eg, anyone who did not follow the skip logic correctly on the paper survey) were removed, and any respondents who stated they were retired in the open responses were removed and recategorized as ineligible.

We categorized the state where respondents practiced into U.S. regions based on U.S. Census Bureau definitions (Northeast, Midwest, South, and West), and Puerto Rico was categorized as "South." We coded participants' practice setting in the following hierarchy if more than one response was selected: university faculty practice, partnership or group, health maintenance organization or staff model, solo or private practice, other. We coded the community type where participants' practice was located in the following hierarchy if more than one response was selected: urban inner city; urban non–inner-city; suburban; midsize town, rural, or military.

If more than one response was provided for the location where induced abortions were performed, we coded abortion location in the following manner: abortion provided only in an ambulatory surgical center or hospital setting, any abortion provided in an outpatient office but not at a Planned Parenthood or specialized clinic, and any abortion in a Planned Parenthood or specialized clinic. We calculated the median number of abortions for each site where abortion was performed among those who provided any abortion.

Statistical tests assumed significance at P value less than .05. Descriptive statistics were calculated separately for respondents who did and did not report providing abortion in the prior year and among participants overall. Comparisons of categorical variables were analyzed using χ^2 tests. Univariable and multivariable logistic regression analyses were performed to estimate odds of providing abortion in the prior 12 months (1 means provided medication or surgical abortion, 0 means did not provide induced abortion) by background characteristics. All variables were used as binary or categorical predictors, with reference groups based on sample size or meaningful comparison. We excluded missing data. We included all independent variables from Table 1 in an initial multivariable regression model. Sequentially, we removed from the model extraneous variables with a P value greater than .2. Age and gender were forced into the model a priori because they were found to be significant predictors of abortion provision in the representative survey of U.S. ob-gyns performed in 2008–2009.[2] The Allendale Investigational Review Board approved this study.

RESULTS

Of the original sample of 1,000 members of the Collaborative Ambulatory Research Network, 18 were found to be no longer an ACOG member or not in practice, and two were unreachable by mail, resulting in a sample of 980 members. Among this sample, 655 respondents provided data (response rate 67%). Nonresponders were similar to respondents in terms of age and geographic region of practice, but slightly more women responded to the survey (61% of respondents vs 55% of nonresponders, P=.06). Of the 655 respondents, 99% reported seeing patients of reproductive age, and of these, 72% reported having a patient in the prior year who needed or wanted an induced abortion. Participants who reported seeing patients of reproductive age who answered the questions on whether they provided medication or surgical abortion (N=597) were included in this analysis. Overall, 515 (86%) took the long version of the survey, and this proportion was similar across geographic regions.

Table 1 shows the demographic characteristics of participants, separated by those who did and did not provide abortion in the prior year. Overall, 23.8% (95% CI 20.5%–27.4%) reported providing any type of induced abortion in the prior year. In univariable analyses, male physicians and physicians residing in the Midwest and South had lower odds of provision compared with female physicians and physicians residing in the Northeast, respectively. Physicians in a university faculty practice had higher odds of provision compared with those in a partnership or group practice, as did physicians practicing in urban or suburban communities compared with those practicing in midsize towns, rural areas, or military settings.

In multivariable regression analysis, controlling for age and gender, those practicing in the Midwest (adjusted odds ratio [AOR] 0.31, 95% CI 0.16–0.60) and the South (AOR 0.22, 95% CI 0.11–0.42) compared with participants living in the Northeast had lower odds of providing induced abortion. Those

Table 1. Background Characteristics of Obstetrician–Gynecologists by Provision of Any Induced Abortion Services in the Prior Year

Characteristic	Total (N=597)	Provided Abortion in Prior Year (n=142)	Did Not Provide Abortion in Prior Year (n=455)	Regression	
				OR	AOR*
All	597 (100)	142 (23.8)	455 (76.2)		
Age (y)					
30 45	153 (25.7)	39 (27.5)	114 (25.2)	1.10 (0.70 1.75)	1.05 (0.64 1.73)
46 60	266 (44.7)	63 (44.4)	203 (44.8)	1.00	1.00
61 or older	176 (29.6)	40 (28.2)	136 (30.0)	0.95 (0.60 1.49)	0.99 (0.59 1.64)
Gender					
Male	234 (39.6)	44 (31.7)	190 (42.0)	0.64 (0.43 0.96)†	0.81 (0.51 1.28)
Female	357 (60.4)	95 (68.4)	262 (58.0)	1.00	1.00
Race and ethnicity					
Asian-Pacific Islander, non-Hispanic	42 (7.1)	15 (10.6)	27 (6.0)	1.87 (0.96 3.65)	NA
Black, non-Hispanic	27 (4.6)	5 (3.6)	22 (4.9)	0.77 (0.28 2.07)	NA
Hispanic	27 (4.6)	5 (3.6)	22 (4.9)	0.77 (0.28 2.07)	NA
White, non-Hispanic	468 (78.8)	107 (75.9)	361 (79.7)	1.00	NA
Other, non-Hispanic	30 (5.1)	9 (6.4)	21 (4.6)	1.45 (0.64 3.25)	NA
Region					
Northeast	68 (11.5)	28 (20.3)	40 (8.9)	1.00	1.00
Midwest	157 (26.6)	27 (19.6)	130 (28.8)	0.30 (0.16 0.56)†	0.31 (0.16 0.60)†
South	198 (33.6)	26 (18.8)	172 (38.1)	0.22 (0.11 0.41)†	0.22 (0.11 0.42)†
West	167 (28.3)	57 (41.3)	110 (24.3)	0.74 (0.41 1.32)	0.71 (0.39 1.29)
Practice setting					
Solo private practice	73 (12.3)	18 (12.8)	55 (12.2)	1.18 (0.65 2.14)	NA
Partnership or group	318 (53.6)	69 (48.9)	249 (55.1)	1.00	NA
HMO or staff model	51 (8.6)	11 (7.8)	40 (8.9)	0.99 (0.48 2.04)	NA
University faculty practice	131 (22.1)	40 (28.4)	91 (20.1)	1.59 (1.00 2.51)†	NA
Other	20 (3.4)	3 (2.1)	17 (3.8)	0.64 (0.18 2.24)	NA
Years in practice					
1 10	91 (16.4)	24 (18.1)	67 (15.9)	1.15 (0.65 2.03)	NA
11 20	189 (34.1)	45 (33.8)	144 (34.2)	1.00	NA
21 or more	274 (49.5)	64 (48.1)	210 (49.9)	0.98 (0.63 1.51)	NA
Practice location					
Urban inner city	107 (18.0)	30 (21.3)	77 (17.0)	2.75 (1.39 5.47)†	2.71 (1.31 5.60)†
Urban non inner-city	182 (30.6)	55 (39.0)	127 (28.0)	3.06 (1.64 5.73)†	2.89 (1.48 5.64)†
Suburban	185 (31.1)	41 (29.1)	144 (31.7)	2.01 (1.06 3.83)†	1.94 (0.99 3.83)
Midsize town, rural, or military	121 (20.3)	15 (10.6)	106 (23.4)	1.00	1.00

OR, odds ratio; AOR, adjusted odds ratio; NA, not applicable (blank cells owing to model inclusion criteria); HMO, health maintenance organization.
Data are n (%) unless otherwise specified.
Columns may not tally to 100% owing to missing values.
* Final adjusted model included age, gender, region, and practice location, n 581.
† Significantly different from reference category at $P<.05$.

practicing in an urban inner city (AOR 2.71, 95% CI 1.31–5.60) or urban non–inner-city area (AOR 2.89, 95% CI 1.48–5.64) had higher odds of providing abortion compared with those in a midsize town, rural area, or who practiced exclusively in the military.

Table 2 shows details of participants' abortion practice in the prior year. Overall, 9.4% provided only surgically induced abortion, 4.0% provided only medication abortion, and 10.4% provided both surgical and medication abortion. Approximately 20% provided surgical abortion in the prior year, with about half of these performing electrical vacuum aspiration, one quarter using manual vacuum aspiration, and one quarter using sharp curettage. Fourteen percent provided medication abortion in the prior year; among these providers, 58.1% used the combined mifepristone–misoprostol regimen, 41.9% used misoprostol alone, and 10.5% used methotrexate and misoprostol. Participants were not specifically asked the gestational age range of patients provided medication abortion.

Participants who completed the long version of the survey and who provided abortion in the prior year gave information about where they provided

Table 2. Abortion Methods Provided by Obstetrician–Gynecologists in the Prior Year (N=597)

Method	n (%)
Provided any induced abortion	142 (23.8)
Provided only surgical induced abortion	56 (9.4)
Provided only medication abortion	24 (4.0)
Provided surgical and medication abortion	62 (10.4)
Provided any surgical induced abortion	118 (19.8)
Dilation and sharp curettage	31 (5.2)
Electrical vacuum aspiration	57 (9.5)
Manual vacuum aspiration	31 (5.2)
Provided any medication abortion	86 (14.4)
Treatment with misoprostol alone	36 (6.0)
Treatment with mifepristone and misoprostol	50 (8.4)
Treatment with methotrexate and misoprostol	9 (1.5)

abortion (n=120). A total of 32.5% reported providing abortion only in an ambulatory surgical center or hospital setting, 47.5% reported providing in an outpatient office but not at a specialized clinic or Planned Parenthood, and 10.8% reported providing at least some abortions at a specialized clinic or Planned Parenthood. However, the number of abortions performed by participants varied by site. The median number of abortions performed in the past year by those who only provided at an ambulatory surgical center or hospital was 5.5, and the median was 8.0 for those who provided in their office but not at a specialized clinic. Among those who provided any abortion at a specialized clinic, the median number of procedures was 112.0 in the prior year (Table 3).

Respondents who reported having patients seeking abortion but did not provide medication abortion in the prior year were asked about reasons why they did not provide (n=368). About one third (34%) cited personal, religious, or moral beliefs against abortion, 19% pointed to practice setting restrictions against abortion provision, and 16% mentioned office staff attitudes. Ten percent said there was no perceived need, and 8% said their patients had access to another provider or they referred out (Table 4). Eleven percent cited a lack of training as the reason for not providing medication abortion, and a similar proportion cited the requirement to stock the medications in their clinic. Nine percent cited the requirement to sign the provider agreement with the manufacturer of mifepristone. Some of the responses in the "other" category, each of which was cited by less than 4% of participants, included community attitudes, not having an ultrasound scanner in the office, lack of surgical backup, and laws and regulations.

When those who did not provide medication abortion but reported having patients seeking abortion were asked whether they would offer the service if they could write prescriptions for the medications, 28% said they would offer medication abortion, 47% said they would not, and 22% said they were not sure (Table 4). The number of respondents who said they would offer medication abortion by prescription (n=102) is more than the number in the survey who reported providing medication abortion in the prior year (n=86). This suggests that the proportion of ob-gyns offering induced medication abortion might increase from 14% currently to as much as 31% if it were not required to stock the medication in one's office.

DISCUSSION

This study aimed to describe induced abortion provision among practicing ob-gyns in the United States and found that 24% of them had performed abortion in the prior year. Factors associated with provision included practicing in the Northeast or West rather than the South or Midwest and practicing in an urban setting. This inequitable geographic distribution is similar to findings in previous research, which may be related to more restrictions on abortion provision in Southern and Midwestern states.[2,7,8]

The proportion of ob-gyns who reported providing induced abortion in our survey was higher than the 14% reported in a national survey conducted in 2008–2009.[2] Our results were similar to a survey of ob-gyns who became board certified between 1998 and 2001, which found that 22% performed an induced abortion in the prior year.[9] The Accreditation Council for Graduate Medical Education has required training in induced abortion in obstetrics and gynecology residency programs since 1996, which may have contributed to an increase in provision.

Among those providing induced abortion in the prior year, approximately one third reported providing the service only in an ambulatory surgical center or hospital setting. Given the safety of providing abortion in an outpatient setting,[10] more research is needed to understand the reasons why ob-gyns choose to provide the service in a hospital. These physicians provided a small number of procedures in the prior year (median of 5.5), which is consistent with national data.[3]

Desai et al recently reported on a survey of ob-gyns in private practice, which found that 7% reported performing an induced abortion in 2013 or 2014.[7] That survey focused on provision of abortions at the physician's office and excluded specialized clinics

Table 3. Site Where Induced Abortion was Provided and Annual Number of Abortions Performed Among Obstetrician–Gynecologists Providing Any Abortions (n=120)*

Site	n (%)	Annual No. of Abortions Performed	
		Median	IQR
Induced abortion provided only in ambulatory surgical center or hospital setting	39 (32.5)	5.5	3 12
Any abortion provided in outpatient office but not at a Planned Parenthood or specialized clinic	57 (47.5)	8.0	3 15
Any abortion provided at a Planned Parenthood or specialized clinic	13 (10.8)	112.0	75 251

IQR, interquartile range.
Columns may not tally to 100% owing to missing values.
* Among respondents who answered long survey.

providing abortion care. About half of the ob-gyns in our survey who provided abortion reported doing so in an outpatient setting, which makes our findings comparable with those of Desai.

Among ob-gyns who reported seeing patients who needed or requested an abortion, the most commonly cited reasons for not providing medication abortion were personal reasons or practice restrictions. These results are similar to a survey of ob-gyns in New Mexico in 2008.[11] Qualitative research has also highlighted how practice restrictions prevent trained physicians from providing the service.[12]

Beyond these personal and practice explanations, some of the reasons for not providing medication abortion could be addressed through training and policy changes. Eleven percent cited a lack of training, suggesting medication abortion teaching in residencies and continuing education might increase uptake of the method. A similar proportion reported that the requirement to stock mifepristone in their clinics was a reason they did not provide the method, and our findings suggest that the number of ob-gyns providing medication abortion might at least double if they could write a prescription for mifepristone. Pharmacy dispensing of Mifeprex by prescription is currently prohibited by the drug's Risk Evaluation and Mitigation Strategy imposed by the U.S. Food and Drug Administration.[6] A recent analysis found that the mifepristone Risk Evaluation and Mitigation Strategy is not justified given the positive safety record of the drug, and the authors argued for its withdrawal.[13] Our survey suggests that the Risk Evaluation and Mitigation Strategy is a barrier to provision of medication abortion, which should add new urgency to the push to remove this medically unnecessary restriction.

Table 4. Perspectives of Obstetrician–Gynecologists Who Do Not Provide Medication Abortion, Among Those Who Had Patients Seeking Abortion (n=368)

	n (%)
Reasons for not providing medication abortion (multiple responses allowed)	
Personal, religious, or moral beliefs against abortion	126 (34.2)
Practice setting restrictions against abortion provision	69 (18.8)
Office staff attitudes	58 (15.8)
Lack of training	41 (11.1)
Requirement to stock medications in clinic	40 (10.9)
No perceived need	36 (9.8)
Requirement to sign agreement with manufacturer of Mifeprex	33 (9.0)
Patients have access to someone else or provider refers out	28 (7.6)
Other	64 (17.4)
Would offer medication abortion to patients if they could write a prescription for mifepristone and misoprostol and patients could obtain both medications at a pharmacy, among those who had not provided induced medication abortion in past year and who had patients seeking abortion	
Would offer medication abortion	102 (27.7)
No	173 (47.0)
Not sure	79 (21.5)

Columns may not tally to 100% owing to missing values.

This study has several limitations. Although the response rate for this survey was 67% and nonresponders were similar to respondents, there is a risk of nonparticipation bias. Of note, participants did not know the survey focused on induced abortion practice when they were invited to participate. Still, it is likely that nonparticipation bias results in an overestimation of abortion provision in this survey. Our survey asked about abortion provision in the prior year, whereas the 2008–2009 survey asked "do you provide abortion services." Although our wording is more precise, it may overestimate provision for physicians who recently stopped offering abortion. The hypothetical question about prescribing mifepristone may overestimate the effect of allowing pharmacy dispensing of the drug, because other barriers, such as practice restrictions and pharmacist refusals, may still limit expansion of medication abortion. In addition, Collaborative Ambulatory Research Network members may represent a subset of more engaged ACOG Fellows who might be more likely to change their practice if the policy regarding mifepristone dispensing were changed.

Quality of induced abortion care depends on all women seeking the service being able to do so in a timely fashion in a safe and effective way. State-based abortion regulations, federal laws restricting provision of medication abortion, individual providers' personal, religious, or moral beliefs, and practice and community factors affect the availability of abortion services and pose barriers to abortion quality. Expanding opportunities for professional development and reversing restrictive state and federal policies may help to improve the quality of abortion care.

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PEER REVIEW HISTORY

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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.

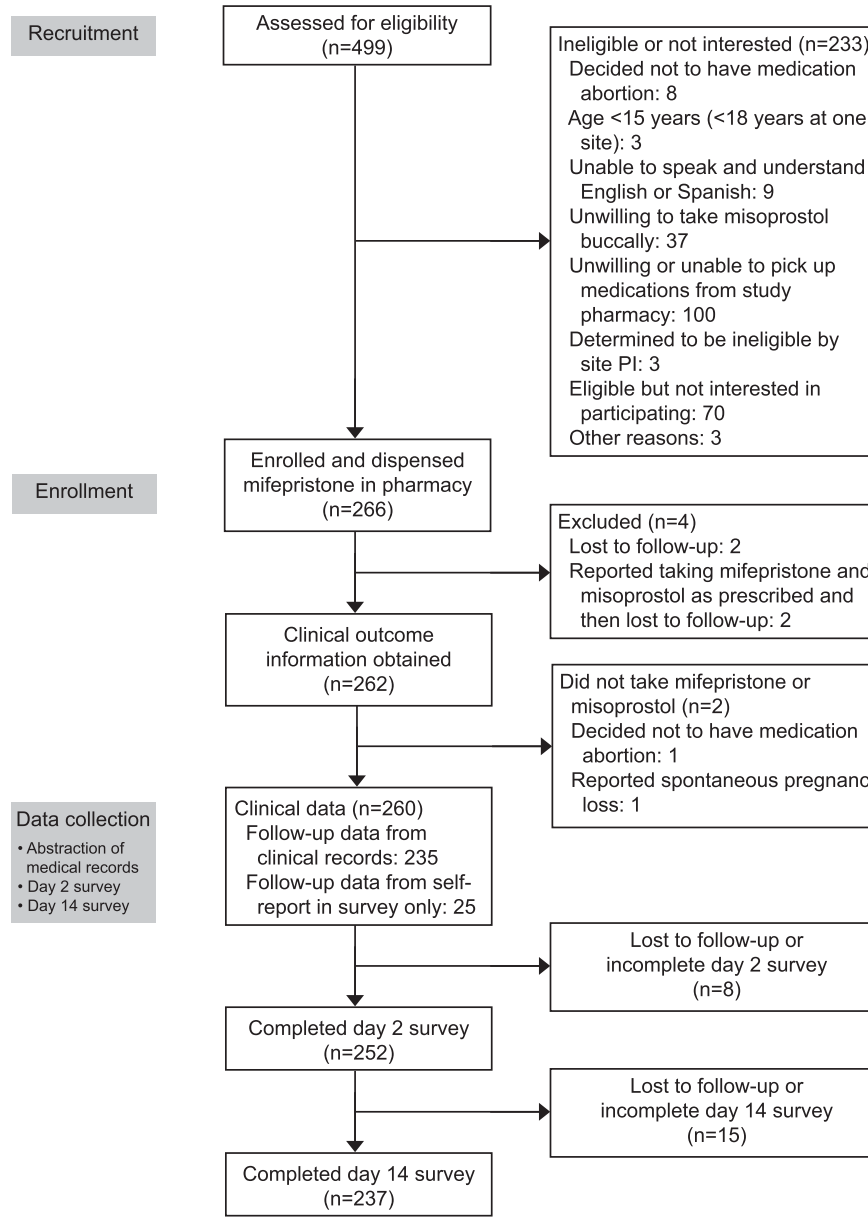

Fig. 1. Medication abortion study flow of patients who received mifepristone from pharmacists. PI, principal investigator.

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.*

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Mail-Order Pharmacy Dispensing of Mifepristone for Medication Abortion After In-Person Screening

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IMPORTANCE Before 2021, the US Food and Drug Administration required mifepristone to be dispensed in person, limiting access to medication abortion.

OBJECTIVE To estimate the effectiveness, acceptability, and feasibility of dispensing mifepristone for medication abortion using a mail-order pharmacy.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study was conducted from January 2020 to May 2022 and included 11 clinics in 7 states (5 abortion clinics and 6 primary care sites, 4 of which were new to abortion provision). Eligible participants were seeking medication abortion at 63 or fewer days' gestation, spoke English or Spanish, were age 15 years or older, and were willing to take misoprostol buccally. After assessing eligibility for medication abortion through an in-person screening, mifepristone and misoprostol were prescribed using a mail-order pharmacy. Patients had standard follow-up care with the clinic. Clinical information was collected from medical records. Consenting participants completed online surveys about their experiences 3 and 14 days after enrolling. A total of 540 participants were enrolled; 10 withdrew or did not take medication. Data were analyzed from August 2022 to December 2023.

INTERVENTION Mifepristone, 200 mg, and misoprostol, 800 µg, prescribed to a mail-order pharmacy and mailed to participants instead of dispensed in person.

MAIN OUTCOMES AND MEASURES Proportion of patients with a complete abortion with medications only, reporting satisfaction with the medication abortion, and reporting timely delivery of medications.

RESULTS Clinical outcome information was obtained and analyzed for 510 abortions (96.2%) among 506 participants (median [IQR] age, 27 [23-31] years; 506 [100%] female; 194 [38.3%] Black, 88 [17.4%] Hispanic, 141 [27.9%] White, and 45 [8.9%] multiracial/other individuals). Of these, 436 participants (85.5%; 95% CI, 82.2%-88.4%) received medications within 3 days. Complete abortion occurred after medication use in 499 cases (97.8%; 95% CI, 96.2%-98.9%). There were 24 adverse events (4.7%) for which care was sought for medication abortion symptoms; 3 patients (0.6%; 95% CI, 0.1%-1.7%) experienced serious adverse events requiring hospitalization (1 with blood transfusion); however, no adverse events were associated with mail-order dispensing. Of 477 participants, 431 (90.4%; 95% CI, 87.3%-92.9%) indicated that they would use mail-order dispensing again for abortion care, and 435 participants (91.2%; 95% CI, 88.3%-93.6%) reported satisfaction with the medication abortion. Findings were similar to those of other published studies of medication abortion with in-person dispensing.

CONCLUSIONS AND RELEVANCE The findings of this cohort study indicate that mail-order pharmacy dispensing of mifepristone for medication abortion was effective, acceptable to patients, and feasible, with a low prevalence of serious adverse events. This care model should be expanded to improve access to medication abortion services.

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Multimedia

Supplemental content

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Medication abortion with mifepristone and misoprostol is safe, effective, and preferred by many patients.[1] Between 2020 and 2023, the proportion of nonhospital abortions in the US that were medication abortion increased from 53% to 63%.[2] This increase likely is related to both the COVID-19 pandemic and the US Supreme Court decision in *Dobbs v Jackson Women's Health Organization*,[3] which eliminated federal protections for abortion. In particular, telehealth provision of medication abortion has recently expanded.[4-7]

Before 2021, the US Food and Drug Administration (FDA) required that, as part of mifepristone's Risk Evaluation and Mitigation Strategy, it be dispensed in person at a clinic, medical office, or hospital.[8] During the COVID-19 public health emergency, the FDA suspended the in-person dispensing requirement, allowing clinicians to provide medication abortion by telehealth. In 2021, the FDA reviewed the evidence and recommended permanently removing the in-person dispensing requirement (noting that it was not necessary to ensure safe and effective use of mifepristone), and explicitly allowed for certified pharmacies to dispense the medication. In 2023, the FDA clarified the components of pharmacy certification.[8]

The in-person dispensing requirement for mifepristone had limited the pool of qualified clinicians able to provide medication abortion. A 2016 to 2017 national survey of obstetrician-gynecologists estimated that 14.4% of those who saw patients seeking abortion care had provided medication abortion during the previous year.[9,10] The study estimated that the proportion of clinicians providing medication abortion would double if they were permitted to prescribe mifepristone through a pharmacy rather than dispense it in-person at a clinic. An important challenge to in-person dispensing for clinicians is the logistics of stocking the medication in their facilities.[10]

The in-person dispensing requirement may be an even greater obstacle for primary care clinicians, including internal medicine and family medicine physicians, who might see only a small number of patients seeking abortion services.[11] Clinicians in primary care settings have faced opposition from colleagues and administrators when seeking institutional support and approval to stock mifepristone onsite.[11,12] Yet, many patients say they would prefer to see their primary care practitioner for an abortion.[13,14] A mail-order dispensing model—in which patients have an in-person visit with the clinician and receive the medications by mail—has the potential to reduce barriers faced by clinicians and achieve patient preferences. However, research on this model has been limited.

In this prospective cohort study, we aimed to estimate the effectiveness, acceptability, and feasibility of providing medication abortion with medications dispensed by a mail-order pharmacy after an in-person eligibility assessment. We compared our findings with published data on medication abortion provided by in-person dispensing of medications. We previously published an interim analysis of the study.[15]

Key Points

Question Is medication abortion with mail-order pharmacy dispensing of mifepristone effective, acceptable, and feasible?

Findings This prospective cohort study included 506 participants and 510 medication abortions (≤63 days' gestation at enrollment) that were provided through mail-order pharmacy dispensing after an in-person eligibility screening; 97.8% were complete abortions and 91.2% of participants reported satisfaction with medication abortion. Serious adverse events were rare (0.6%) and none were associated with mail-order dispensing.

Meaning These findings support the US Food and Drug Administration's decision to remove the in-person dispensing requirement for mifepristone.

Methods

This study was conducted under an FDA Investigational New Drug application and was registered with ClinicalTrials.gov.[16] The institutional review boards of the University of California San Francisco, Albert Einstein College of Medicine (New York, New York), Christiana Care (Newark, Deleware), Kent Hospital (Warwick, Rhode Island), Lifespan (Providence, Rhode Island), and Alameda Health System (Oakland, California) approved the study. Site investigators completed the mifepristone prescriber agreement form, and patients completed the patient agreement form.[8] Trained staff obtained written informed consent from interested and eligible patients. The design of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[17]

Study Design and Participants

From January 2020 through May 2022, with a pause from March to June 2020 due to the COVID-19 pandemic, we enrolled patients in a prospective cohort study at 11 clinical sites in 7 US states (California, Colorado, Delaware, Georgia, New York, Pennsylvania, and Rhode Island). The sites included 5 abortion clinics and 6 primary care clinics, 4 of which had not provided abortion care before the study. The study was advertised at meetings and on listservs that included primary care and abortion practitioners across the country. Interested sites were informed that the study would provide training in medication abortion (if applicable) and support integrating the service into their practice. Sites with sufficiently large eligible patient populations and administrative support were selected to participate.

Services were provided by physicians and advanced practice clinicians specializing in family medicine, internal medicine, obstetrics and gynecology, or pediatrics. Participants were eligible for the study if they were seeking and eligible for medication abortion according to the FDA-approved mifepristone label[18]; willing to receive medications from a mail-order pharmacy; willing to use misoprostol buccally as described in the labeling; able to read and speak English or Spanish; willing to be contacted by email or phone; and pregnant with a gestational duration of 63 or fewer days (to reduce the possibility that shipping delays would be associated with mifepristone being used after the FDA limit of 70 days' gestation). Depending on state parental consent requirements, participants were eligible if

they were at least 15 (8 sites), 16 (1 site), or 18 years of age (2 sites).

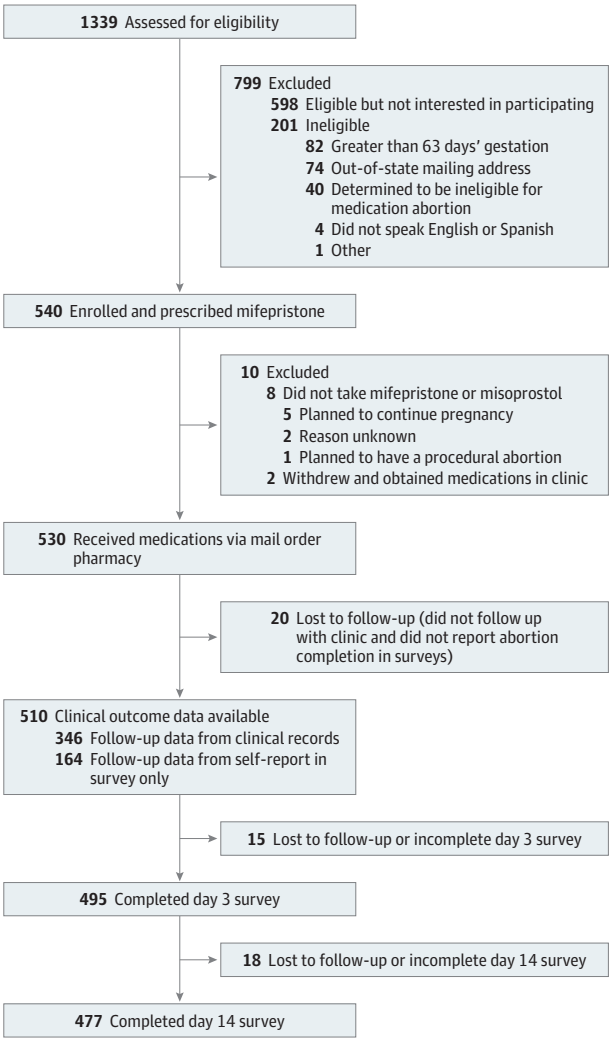
Study design, recruitment, and procedures were published previously.[15] Clinicians evaluated patients in person for medication abortion eligibility and determined gestational duration according to the patients' self-reported history confirmed by physical examination or ultrasonography imaging, consistent with standard protocols.[19,20] Consenting participants received instructions on medication use and were scheduled for follow-up to confirm abortion completion. Follow-up options included ultrasonography, serum human chorionic gonadotropin measurement, or a telephone call to assess symptoms followed by home urine pregnancy testing. Participants received gift cards at enrollment ($15) and after completing each of 2 surveys ($25). After consenting, participants were informed that the study would pay for the cost of clinical visits, medications, pharmacy dispensing fees, and shipping.

Clinic staff assessed 1339 patients for eligibility and enrolled 540 participants (**Figure**). Two participants withdrew from the study and obtained medications in clinic, and 538 participants received medications via mail-order pharmacy dispensing. Eight participants did not take the medications they received in the mail. Of the remaining 530 participants, 20 (3.8%) did not follow up with the clinic nor complete survey questions related to abortion completion; they were excluded from the analysis. Four patients participated in the study twice for 2 abortions and were counted twice in the study flow diagram because the unit of analysis was abortions (Figure).

On enrollment day, clinicians prescribed mifepristone, 200 mg, and misoprostol, 800 µg, to a mail-order pharmacy. At the clinician's discretion, some also prescribed analgesics, antibiotics, antiemetics, pregnancy tests, and contraceptives. If it was anticipated that the patient would take mifepristone at 63 days' gestation or later, some clinicians prescribed a second dose of misoprostol, 800 µg, to take 4 hours after the first dose. The mail-order pharmacy processed prescriptions according to a "next-day delivery" workflow and shipped packages (unmarked other than the pharmacy return address) to participants.

On days 3 and 14 after enrollment, we sent participants email requests to complete online surveys (Qualtrics LLC) regarding their experience receiving the package, taking the medications, and having the abortion. Participants provided demographic information, including self-reported race and ethnicity, at the end of the first survey. Six or more weeks after enrollment, personnel from each site entered deidentified data on visits and any other contact with participants into electronic forms (REDCap, Vanderbilt University). Details regarding information collected in each survey were published previously.[15] We used survey and medical record data to identify abortion outcomes and adverse events (AEs) occurring within 6 weeks of enrollment, including any unscheduled visits for symptoms possibly related to the medication abortion. Serious AEs were defined as death, hospitalization, blood transfusion, or surgery.[21]

Figure. Study Flow of Patients Seeking Medication Abortion Who Were Evaluated in Person and Received Mifepristone From a Mail-Order Pharmacy, 2020 to 2022



The unit of analysis was an abortion (4 patients were enrolled in the study twice).

Study Outcomes

Our primary outcomes included effectiveness and acceptability. We evaluated medication abortion effectiveness as the proportion of abortions that were complete (with medications only) within the 6-week study follow-up period. Patient acceptability was measured by the proportion of patients who reported that they were satisfied or very satisfied with the medication abortion, and by the proportion reporting they would use the mail-order service again if they needed another abortion. We also measured the proportion who reported they were very satisfied with the mail-order model. Secondary outcomes included feasibility of the model, determined by the proportion of patients who reported timely (within 3 days following enrollment visit) and confidential delivery of medications, as well as safety outcomes (ie, serious AEs).

Table 1. Sociodemographic Characteristics of Study Participants Having Medication Abortion and Receiving Mifepristone From a Mail-Order Pharmacy, 2020 to 2022[a]

Characteristic	No. (%)
Total participants	506
Age group, y	
15-19	30 (5.9)
20-24	144 (28.5)
25-29	161 (31.8)
≥30	171 (33.8)
Age, median (IQR), y	27 (23-31)
Race and ethnicity	
Black	194 (38.3)
Hispanic	88 (17.4)
White	141 (27.9)
Multiracial/other race[b]	45 (8.9)
Missing data	38 (7.5)
Educational level	
High school or less	170 (33.6)
Some college or professional school	206 (40.7)
College or advanced degree	112 (22.1)
Missing data	18 (3.6)
Parity	
Nulliparous	189 (37.4)
Parous	317 (62.6)
Prior abortion experience	
None	249 (49.2)
Medication abortion	149 (29.4)
Procedural abortion only	93 (18.4)
Missing data	15 (3.0)

[a] Among participants who took medications and had clinical outcome data available (unit of analysis is the number of individuals in the study).

[b] Other race included Cape Verdean; Native Hawaiian or Pacific Islander; American Indian or Alaska Native; and those who did not report this information.

Statistical Analysis

Given low loss to follow-up, we excluded participants with missing outcome data. We calculated binomial 95% CIs for the main outcomes. To assess how the effectiveness and acceptability of the mail-order model compared with that of in-person dispensing, we calculated risk differences with corresponding 95% CIs and *P* values using a statistical test on the equality of proportions for effectiveness and acceptability comparing our sample estimates with published estimates of patients obtaining mifepristone in person. A review of US medication abortion trials with in-person dispensing (N = 16 794)[18] included in the mifepristone label found a pooled estimate of effectiveness of 97.4%. A meta-analysis of 8 studies found that an average of 88.4% of those who had a medication abortion and took misoprostol at home (N = 3138) reported being "satisfied or highly satisfied."[22] A study of medication abortion up to 63 days' gestation (N = 1080) found that 89.7% of patients would use medication abortion again.[23] If the lower bounds of the 95% CIs of the risk differences in our estimates were no lower than −0.05 (or 5% worse), we concluded that the mail-order dispensing model was comparable with in-person dispensing.

We modeled satisfaction with the mail-order model (ie, very satisfied compared with all others) using mixed-effects multivariable logistic regression; variables included participant age, race and ethnicity, education, parity, prior abortion experience, gestational duration, satisfaction with package delivery time, package condition, and whether confidentiality was maintained during shipping. We included race and ethnicity, with White as the reference category because we hypothesized that experiences with racism in health care settings, including in the context of the current abortion, may affect satisfaction, and because individuals of other race and/or ethnicity have been shown to be more likely to experience race-based discrimination in health care.[24] We adjusted for clustering by clinic site as a random effect in mixed-effects regression models.

The target sample size was based on the primary outcome measures of effectiveness and acceptability, assuming 10% loss to follow-up, 10% adjustment for clustering, a 5% noninferiority margin, and a 2-sided $\alpha = .05$. The planned sample size was a minimum of 440 participants, which would provide a final analytic sample of approximately 400 patients and 98%, 79%, and 77% power to assess the proportion with a complete abortion, the proportion who would use the mail-order service again, and the proportion who reported being satisfied or very satisfied with the medication abortion, respectively. Data were analyzed from August 2022 to December 2023 using Stata, release 17.0 (StataCorp LLC).

Results

We obtained clinical outcome data from clinic records and self-reported survey data for 510 abortions among 506 participants (median [IQR] age, 27 [23-31] years; 506 [100%] female; 194 [38.3%] Black, 88 [17.4%] Hispanic, 141 [27.9%] White, and 45 [8.9%] multiracial/other individuals). Additional self-reported participant characteristics are presented in **Table 1**.

The median (range) number of participants per study site was 18 (2-209) overall, with 48 (26-209) among abortion sites and 7 (2-18) among primary care sites. Of 510 abortions, we obtained completed day-3 survey data for 495 participants (97%) and day-14 survey data for 477 (94%).

All participants received their medications by mail and 436 (85.5%; 95% CI, 82.2% to 88.4%) received the package within 3 days of enrollment (**Table 2**). The pharmacy sent a second package to 5 participants who experienced delivery delays. Delivery time was reported to be reasonable by 467 recipients (94.3%), whereas 27 (5.5%) reported it was too long (**Table 3**). The package was reported to be in good condition by 482 participants (97.4%) and damaged by 12 (2.4%); none reported damage to the medications. In addition, 486 respondents (98.2%) reported that their confidentiality was maintained during the shipping and delivery process; 8 reported that their confidentiality was compromised when another person saw the

Table 2. Clinical Outcomes and Regimen for Participants Having Medication Abortion and Receiving Mifepristone From a Mail-Order Pharmacy, 2020 to 2022 (N = 510)[a]

Clinical outcome variables	No. (%)
Recruitment site	
Primary care clinic	47 (9.2)
Abortion clinic	463 (90.8)
Gestational duration at initial clinic visit, d[b]	
≤49	360 (70.6)
50-56	93 (18.2)
57-63	57 (11.2)
Medication delivery time (from prescription to package delivery), d	
≤3	436 (85.5)
4-7	71 (13.9)
>7	3 (0.6)
Gestational duration at date of taking mifepristone, d	
≤49	260 (51.0)
50-56	136 (26.7)
57-63	72 (14.1)
64-70	29 (5.7)
>70	3 (0.6)
Missing data	10 (2.0)
Gestational duration at mifepristone, median (IQR), d	49 (44-55)
Route of misoprostol administration	
Buccal	486 (95.3)
Vaginal	5 (1.0)
Missing data	19 (3.7)
Interval between mifepristone and misoprostol, h	
<24	5 (1.0)
24-48	491 (96.3)
Missing data	14 (2.7)
Initial dose of misoprostol, 800 µg	483 (94.7)
Missing data	27 (5.3)
Abortion outcome	
Complete with medications only	499 (97.8)
With repeat dose of misoprostol[c]	27 (5.3)
Unsuccessful medication abortion[d]	11 (2.2)
Incomplete abortion	5 (1.0)
Ongoing pregnancy	6 (1.2)
Confirmation of abortion completion, total No.	499
Followed-up with study clinic, No.	336
Ultrasonography	121 (36.0)
Serial serum human chorionic gonadotropin testing	14 (4.2)
Negative urine pregnancy test (in clinic)	9 (2.7)
Clinical history and home urine pregnancy test (telephone visit)	141 (42.0)
Clinical history alone (telephone visit)	51 (15.2)
No follow-up with clinic but indicated completion on survey, No.	163
Negative result of home urine pregnancy test	117 (71.8)
Reported that clinic said abortion was complete	4 (2.5)
Reported an ultrasonography	2 (1.2)
Reported completion based on history alone[e]	40 (24.5)
Normal menstrual period returned	4 (2.5)
No more pregnancy symptoms	33 (20.2)
Other, eg, heavy bleeding/passed tissue	2 (1.2)
Self-reported but no reason given	6 (3.7)

[a] Among participants who took medications and had clinical outcome data available. Includes 4 participants who had 2 abortions in study (unit of analysis is the number of abortions).

[b] Ultrasonography was used to assess gestational duration in 487 participants; 23 had only clinical assessment with physical examination.

[c] Nine participants were prescribed a second dose initially, and 18 were prescribed a second dose at follow-up for incomplete abortion.

[d] All had a procedural abortion except 1 participant who chose to continue the pregnancy.

[e] Some participants reported more than 1 option.

Table 3. Acceptability and Satisfaction at Day 3 Survey Among Study Participants Having Medication Abortion and Receiving Mifepristone From a Mail-Order Pharmacy, 2020 to 2022 (n = 495)[a]

Acceptability variables	No. (%)
Satisfaction with receiving medications by mail	
Very satisfied	452 (91.3)
Somewhat satisfied	26 (5.3)
Neither satisfied nor dissatisfied	7 (1.4)
Somewhat dissatisfied	4 (0.8)
Very dissatisfied	6 (1.2)
Acceptability of medication delivery time	
Reasonable	467 (94.3)
Too long	27 (5.5)
Missing data	1 (0.2)
Condition of package	
Good condition (no evidence of tampering)	482 (97.4)
Damaged (eg, opened, punctured, crushed)	12 (2.4)
Missing data	1 (0.2)
Location where package was received	
Home address	448 (90.5)
Family, friend, or partner's house	18 (3.6)
Study clinic	4 (0.8)
Work address	2 (0.4)
Somewhere else (not specified)	16 (3.2)
Missing data	7 (1.4)
Confidentiality maintained during shipping	
Yes	486 (98.2)
No, confidentiality was compromised	8 (1.6)
Missing data	1 (0.2)
Adequate information received from clinic	
Yes	494 (99.8)
No, I would have liked more information	1 (0.2)
Current vs previous medication abortion experience (among those who had previous medication abortion), No.	150[b]
This time was better	82 (54.7)
Same	54 (36.0)
Last time was better	4 (2.7)
Not sure	6 (4.0)
Missing data	4 (2.7)

[a] Among participants who had clinical outcome data available and completed the day 3 survey (unit of analysis is the number of abortions).

[b] One participant who enrolled twice reported prior medication abortion experience.

package (n = 5), opened the package (n = 2), or observed their pregnancy symptoms or medication adverse effects (n = 3).

Complete medication abortion occurred for 499 of 510 cases (97.8%; 95% CI, 96.2% to 98.9%), including for 27 participants (5%) who took an additional dose of misoprostol. This compares favorably with a complete abortion rate of 97.4% cited in the mifepristone label[18] (risk difference, 0.004; 95% CI, −0.009 to 0.017; *P* = .58). eTable 1 in Supplement 1 shows effectiveness by gestational duration. Eleven participants (2.2%) had an unsuccessful medication abortion; 10 obtained a vacuum aspiration for incomplete abortion (n = 5) or for ongoing pregnancy (n = 5). One participant chose to continue the pregnancy after taking the medications and subsequently reported the uncomplicated delivery of a healthy newborn.

There were 24 AEs (4.7%; 95% CI, 3.0%-7.0%) for which patients sought care for symptoms that were possibly, probably, or definitely related to the medication abortion. These included unscheduled visits for symptoms such as bleeding, pain, nausea, vomiting, infection, and diarrhea. Seventeen AEs included an emergency department visit; in 10 of these visits, the patient received treatment such as analgesics, antibiotics, intravenous fluids, or vacuum aspiration for incomplete abortion. Three serious AEs occurred (0.6%; 95% CI, 0.1%-1.7%), all of which involved hospitalization: 1 participant received a blood transfusion for hemorrhage with incomplete abortion, 1 received antibiotics for an infection with incomplete abortion, and 1 received no treatment. There were no AEs related to mail-order pharmacy dispensing.

Nearly all participants (478 of 495 [96.6%; 95% CI, 94.6 to 98.0]) reported they were very satisfied (91.3%) or somewhat satisfied (5.3%) with mail-order dispensing (Table 3). Of 477 participants, 431 (90.4%; 95% CI, 87.3% to 92.9%) reported that they would use it again for a future medication abortion if needed; this proportion is similar to a published

Table 4. Acceptability and Satisfaction at Day 14 Survey Among Participants Having Medication Abortion and Receiving Mifepristone From a Mail-Order Pharmacy, 2020 to 2022 (n = 477)[a]

Acceptability variables	No. (%)
Overall satisfaction with medication abortion	
Very satisfied	382 (80.1)
Somewhat satisfied	53 (11.1)
Neither satisfied nor dissatisfied	31 (6.5)
Somewhat dissatisfied	6 (1.3)
Very dissatisfied	5 (1.0)
Would recommend medication abortion to a friend	
Yes	431 (90.4)
No	14 (2.9)
Not sure	32 (6.7)
Would recommend mail-order dispensing to a friend	
Yes	447 (93.7)
No	5 (1.0)
Not sure	23 (4.8)
Missing data	2 (0.4)
Would prefer to receive medications by mail for future medication abortion	
Yes	431 (90.4)
No	20 (4.2)
Not sure	26 (5.5)

[a] Among participants who had clinical outcome data available and completed the day 14 survey (unit of analysis is the number of abortions).

estimate[23] indicating that 89.7% of individuals accessing the service with in-person dispensing said they would use medication abortion again (risk difference, 0.007; 95% CI, −0.02 to 0.04; P = .67).

Participants who were less than very satisfied with mail-order dispensing (n = 43; Table 3) provided open-ended responses describing what could be improved. Approximately half said the timing of delivery could be more aligned with expectations set by the clinic. Some suggested providing patients with package-tracking information. Three participants said they would have preferred more privacy in the delivery process (eg, better package placement, hand-to-hand delivery, and avoiding the word "abortion" on documents included in the package).

Regarding the medication abortion experience overall, 91.2% (435 of 477; 95% CI, 88.3%-93.6%) said they were very satisfied (80%) or satisfied (11%) (**Table 4**), which is similar to a published estimate[22] in which satisfaction of medication abortion with in-person dispensing was 88.4% (risk difference, 0.028; 95% CI, 0.001-0.055; P = .06). In multivariable regression analysis, those who reported the delivery time was too long (adjusted odds ratio, 0.04; 95% CI, 0.01-0.10) or that confidentiality was compromised (adjusted odds ratio, 0.05; 95% CI, 0.01-0.32) had significantly lower odds of reporting satisfaction with mail-order dispensing (eTable 2 in Supplement 1).

Discussion

We found that medication abortion with mail-order pharmacy dispensing of medications after an in-person assessment for eligibility was effective and acceptable to patients with comparable findings to other studies of medication abortion with in-person dispensing.[18,22,23] The mail-order model was feasible, with 85.5% of participants receiving the medications within 3 days and 99.4% within 7 days. Although the study was not powered to estimate safety outcomes, we observed a low prevalence of serious AEs (0.6%, 95% CI 0.1%-1.7%). This is similar to a report of 11 319 medication abortions with in-person dispensing in California in 2009 to 2010 that found only 0.3% had a major complication.[25]

This study adds to a growing body of literature demonstrating that medication abortion can be provided safely and effectively using models of care that do not involve a clinician dispensing mifepristone in person. Another US study found that medication abortion with mifepristone dispensed from a brick-and-mortar pharmacy was effective and acceptable to patients with a low prevalence of AEs.[26] Other US studies of medication abortion with telehealth evaluation for eligibility and medications mailed either by the clinician or using a mail-order pharmacy similarly have found these models to be effective (estimates of complete abortion range from 93% to 99%), acceptable to patients (satisfaction ranges from 96% to 100%), and safe (serious AEs range from 0% to 1%).[6,27-32] This body of research supports the FDA decision in 2021 to permanently remove the in-person dispensing requirement for mifepristone.

Although overall satisfaction with mail-order dispensing was high, participants noted areas for improvement, primarily related to meeting expectations regarding the timing and tracking of medication delivery. Mechanisms for ensuring speedy and confidential delivery are already used by major shipping companies, including for the delivery of pharmaceuticals, and should be no different for abortion medications. A recent analysis of a retrospective cohort study[33] found that mailing pills to patients was not significantly associated with

delays in obtaining medication abortion compared with receiving pills in the clinic.

With the severe restrictions on abortion care imposed since the *Dobbs* decision,[3] pharmacy dispensing of mifepristone has an important role to play in improving access. For both patients in states where abortion remains legal and those in states with restrictions who must travel for services, expanded access to medication abortion may reduce delays to care and congestion at abortion clinics where procedural abortion is provided.[34] Pharmacy dispensing also could enable more practitioners, including primary care clinicians, to provide medication abortion by removing the requirement to stock mifepristone. Offering this service in the primary care setting, where communities that historically experience barriers to care can most easily access reproductive health services, could help to normalize medication abortion and improve continuity of care, as well as expand access.[35] So far, only a small number of brick-and-mortar pharmacies have become certified to dispense mifepristone.[36] Mail-order pharmacy dispensing could offer convenience and timely access to abortion medicines for patients who live far from certified brick-and-mortar pharmacies.

When combined with telehealth services for eligibility screening and counseling, mail-order dispensing of mifepristone allows for fully remote medication abortion. Although not the focus of the present study, fully remote medication abortion could likely expand access to a greater extent than models requiring in-person eligibility assessment. A recent analysis[37] found that telehealth provision of medication abortion helped certain patients obtain a timely abortion, including younger patients, those experiencing food insecurity, those living in rural areas, or those who averted traveling more than 100 miles to the nearest abortion clinic.

Strengths and Limitations

This study has several strengths, including recruiting from both established abortion clinics and primary care clinics new to abortion care in a range of geographic settings, as well as the low loss to follow-up (3.8%). The study also has limitations. The intervention was not randomized, which may limit generalizability. Clinical sites that agreed to participate had at least 1 motivated clinician and a supportive administrative environment and were typically located in states with relatively few abortion restrictions. Patients who agreed to participate in the study were open to mail-order dispensing, and this option may not be acceptable or feasible for all patients. The study also was not powered to precisely estimate safety outcomes. In addition, satisfaction with services may be overestimated due to social desirability bias.

Conclusions

The findings of this cohort study on the effectiveness and acceptability of medication abortion using a mail-order pharmacy to dispense mifepristone were comparable with published studies of in-person dispensing. This study adds to the substantial body of evidence supporting the FDA decision to remove the in-person dispensing requirement for mifepristone. Building on this policy change, efforts are needed to expand pharmacy dispensing of mifepristone and telehealth provision of medication abortion, and to test other innovative strategies to reduce barriers to this critical element of comprehensive health care.

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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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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."

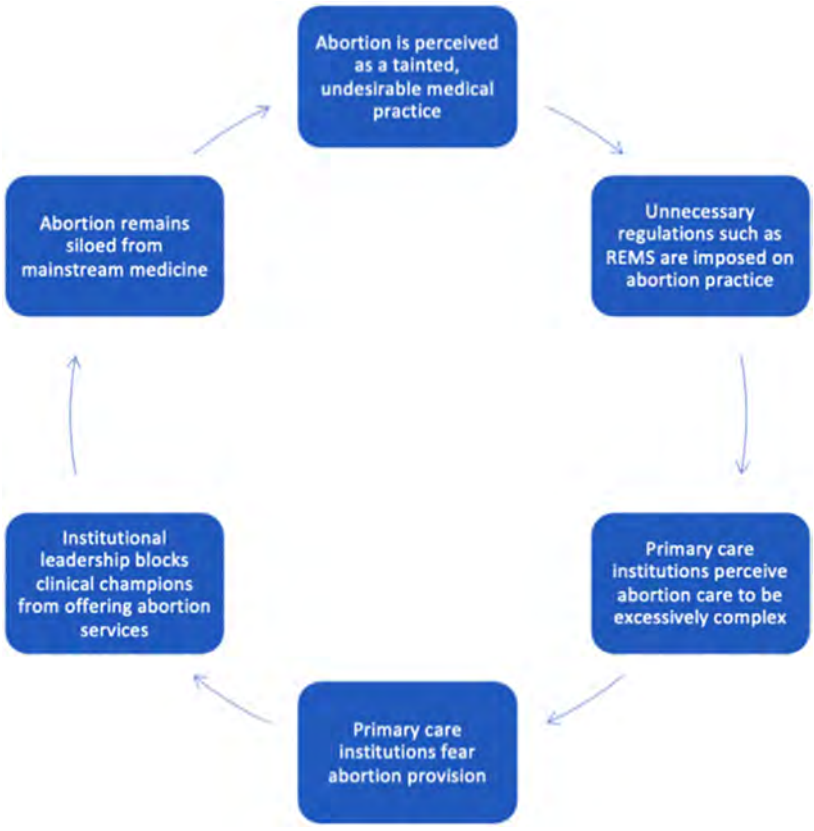

Fig. 2. Cycle of abortion stigmatization in primary care.

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-

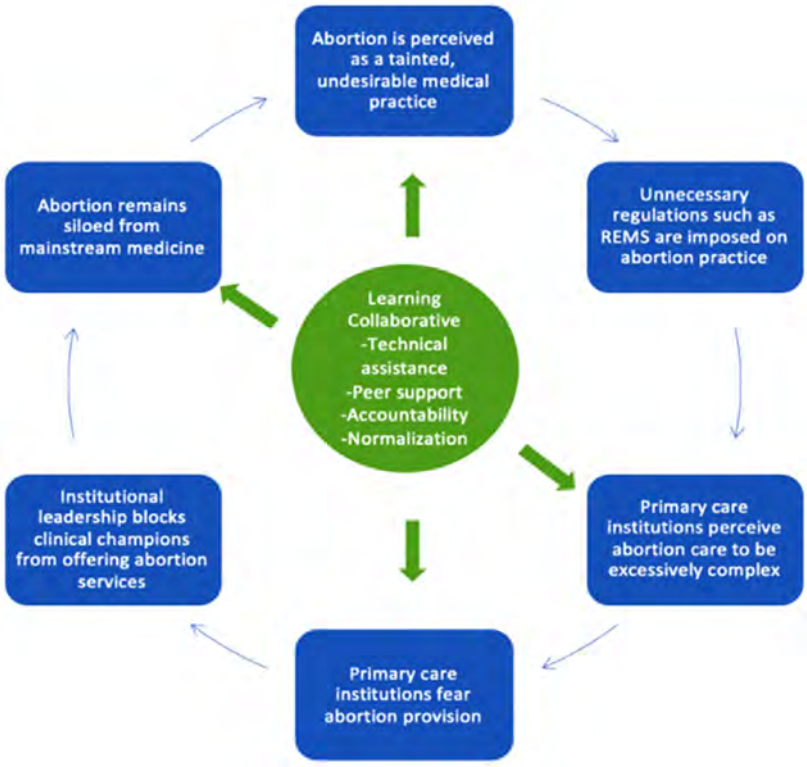

Fig. 3. Cycle of stigmatization of abortion in primary care—Hypothesized impact of a learning collaborative intervention.

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.

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Options for Women with Unintended Pregnancy

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Unintended pregnancy refers to unwanted, unplanned, or mistimed pregnancies. One-half of all pregnancies in the United States are unintended, and family physicians are often asked to provide counseling, support, and resources for women with unintended pregnancies. Options include carrying the infant to term and raising the child, carrying the infant to term and choosing adoption, or having an induced abortion. Family physicians should be equipped to direct women who choose to raise the infant to appropriate care and resources. Most U.S. women do not choose adoption, but there are multiple resources for women interested in this option. Physicians should not broker adoptions, match potential parents with mothers, or adopt children of their own patients. Induced abortion is performed in the first or second trimester of pregnancy. Medical management is comparable with surgical management, and both methods are safe and effective. Combination regimens with mifepristone and misoprostol are the most effective medical methods. Dilation and curettage and vacuum aspiration are the most common surgical methods. (*Am Fam Physician*. 2015;91(8):544-549. Copyright © 2015 American Academy of Family Physicians.)

▶ **See related Curbside Consultation on page 574.**

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 521.

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▶ **Patient information**: A handout on this topic, written by the authors of this article, is available at http://www.aafp.org/afp/2015/0415/p544-s1.html.

Unwanted, unplanned, or mistimed pregnancies are considered unintended. According to the 2006-2008 National Survey of Family Growth, approximately one-half of all pregnancies in the United States are unintended, with 29% mistimed and 19% unwanted; 43% of these pregnancies end in abortion.[1] Each year, unintended pregnancies are associated with more than $11 billion in health care spending.[1] Unintended pregnancies can be stressful, and family physicians can help by providing unbiased medical information and options to women and their families.

Risk Factors

Understanding risk factors for unintended pregnancy can assist family physicians during contraceptive and preconception counseling. In a survey of more than 1,300 women in 13 family planning clinics, risk factors for unprotected intercourse included difficulty obtaining contraceptives, less than a college education, age 20 to 24 years, and black race.[2] Additionally, in observational data obtained from nearly 1,500 females 14 to 40 years of age, women with unintended pregnancy had less social support (mean number of friends = 2.5 vs. 3.0; $P = .005$), more depressive symptoms (67% vs. 49%; $P < .05$), and a higher level of perceived current stress (6.9 vs. 5.6 on a 10-item scale; $P < .001$) compared with women with intended pregnancy.[3] Childhood sexual assault and current depressive symptoms were also positively associated with reports of sadness and the desire to abort. Women with a history of intimate partner violence have increased odds of unintended pregnancy (odds ratio [OR] = 1.69; 95% confidence interval [CI], 1.53 to 1.86) and abortion (OR = 2.68; 95% CI, 2.34 to 3.06).[4] Factors associated with unintended pregnancy include obtaining less than the recommended amount of preconception folic acid (OR = 2.39; 95% CI, 1.7 to 3.2), prenatal tobacco use (OR = 2.03; 95% CI, 1.5 to 2.9), postnatal tobacco use (OR = 1.86; 95% CI, 1.35 to 2.55), postpartum depression (OR = 1.98; 95% CI, 1.48 to 2.64), and being less likely to initiate first-trimester prenatal care (OR = 0.34; 95% CI, 0.3 to 0.5).[5]

Initial Evaluation

Pregnancy is often suspected based on results from a home pregnancy test, and is confirmed in a clinic with a urine or blood test. An accurate estimated gestational age

should be calculated. For women with a certain last menstrual period (LMP), this can be done using Naegele's rule (LMP + 7 days + 9 months),[6] a paper wheel, or an electronic app. In a recent study, only 35% of paper wheels were accurate, whereas 100% of electronic apps calculated the correct date.[7] Alternatively, ultrasonography can be used to calculate or confirm the estimated gestational age. First-trimester ultrasonography using crown-rump measurement is the most accurate means for ultrasound dating of pregnancy.[8]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Physicians should provide unbiased, medically accurate information regarding options for women with unintended pregnancy.	C	9, 15, 16
Physicians should not broker adoption, match prospective parents with pregnant women, or adopt children from their patients.	C	21
Medical and surgical abortions are comparably safe and effective.	A	10-14, 22-28, 30, 31
For first-trimester medical abortion, 200 mg of oral mifepristone (Mifeprex) plus 800 mcg of misoprostol (Cytotec) given vaginally, buccally, or sublingually is superior to 600 mg of oral mifepristone plus 400 mcg of oral misoprostol.	A	27
Combination regimens are superior to single agents for medical abortions.	A	23, 25-27

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

Options for Unintended Pregnancy

There are three options for any pregnancy: carrying the fetus to delivery and raising the child, carrying the fetus to delivery and choosing adoption, or having an induced abortion. The physician's role is to help patients make an informed decision and guide them to available resources, particularly when patients choose adoption or abortion. Physicians should approach the discussion in a nonjudgmental way and respect the decision and rights of the patient. They should avoid coercion in any form, and they must present impartial and medically accurate characterizations of reproductive options.[9] Questions regarding the safety of induced abortion are common *(Table 1)*.[10-14] Access to follow-up care is essential, and patients should realize they can change their mind during the pregnancy.[15]

Table 1. Questions Regarding the Safety of Induced Abortion

Question	*Relevant research*
Does induced abortion increase the risk of breast cancer?	A meta-analysis of 13 prospective studies involving 44,000 women who had an induced abortion vs. women with no history of abortion showed no difference in the incidence of breast cancer (relative risk = 0.93; 95% confidence interval, 0.89 to 0.96; *P* = .0002).[10]
Is induced abortion associated with poor long-term psychological outcomes?	Inpatient or outpatient psychiatric contact was measured before and after induced abortion in 84,620 women for up to 12 months; similar incidence was noted before and after the procedure (14.6 contacts per 1,000 person-years vs. 15.2 per 1,000 person-years, respectively).[11] A systematic review of 26 studies concluded that high-quality studies consistently do not show an association between induced abortion and long-term mental health sequelae.[12]
Is induced abortion more dangerous than live childbirth?	Between 1998 and 2005 in the United States, mortality among women who delivered live neonates was 8.8 per 100,000 live births, whereas the mortality rate associated with legal abortion was 0.6 per 100,000 abortions.[13] The relative risks of morbidity with live birth vs. induced abortion were significantly higher for postpartum hemorrhage, obstetric infections, hypertensive disorders, antepartum hemorrhage, and anemia.[13]
Will an abortion adversely affect future pregnancies?	Among more than 11,000 pregnancies in women with a history of first-trimester medical or surgical abortion, there was no associated increased risk of ectopic pregnancy, spontaneous abortion, preterm birth, or low birth weight.[14]

Information from references 10 through 14.

CONSCIENTIOUS REFUSAL

When caring for women with unintended pregnancy, physicians may exercise conscientious refusal if they are morally opposed to a patient's decision. In a policy letter on reproductive decisions, the American Academy of Family Physicians (AAFP) states that a physician should not be compelled to perform any act that violates his or her good judgment or personally held moral principles, and may withdraw from the case as long as withdrawal is consistent with good medical practice.[16] However, the AAFP also states that a woman who is considering an elective abortion should be adequately informed about the potential health risks of abortion and continued pregnancy. The physician should provide her with information about (1) financial and other assistance available to both her and the child; (2) the availability of licensed or regulated adoption agencies if she chooses not to keep the child; and (3) the availability of safe, legal abortion services if she chooses not to continue the pregnancy; or the physician should identify resources where such information can be obtained.[16] In addition, the American College of Obstetricians and Gynecologists recommends that physicians who are not willing to provide specific reproductive services should have referral processes in place to provide for transfer of care in a timely manner. Physicians should give advance notice of their personal moral commitments and should not advocate or argue their position to patients.[9]

RAISING THE INFANT

Family physicians can have an important role in assisting women who decide to continue the pregnancy and raise the infant. A physician's role may be not only to provide prenatal care, but also to direct the patient to resources that may help her and her family with the pregnancy and the subsequent care of the infant. Physicians can familiarize themselves with local public health agencies to help with medical, financial, and social or spiritual resources. Because of some patients' socioeconomic limitations, coordination of transportation and care may be necessary.

ADOPTION

According to data from the National Survey of Family Growth, voluntary placement of children for adoption is relatively rare in the United States. Data from their 1995 survey show that less than 1% of children born to never-married women were placed for adoption.[17] The percentage for white women is higher than for black women (1.7% vs. near 0%, respectively). Extrapolation of these percentages to the 1.4 million births to unmarried women in 2003 would mean that fewer than 14,000 children were placed for adoption.[17]

Most adoption research has focused on unmarried teenagers. Post-birth surveys show that women with higher education levels and high career or educational aspirations are more likely to choose adoption.[18] Women who had positive personal experiences with adoption are more willing to place their child with adoptive parents.[18,19] Pregnant teenagers whose boyfriends or mothers wanted them to choose adoption were much more likely to do so. In addition, women who expected little assistance with child care from their mothers were more likely to choose adoption.[20]

Adoption occurs through licensed private or state-run adoption agencies or through informal transfer of care that may not include formal relinquishment of all parental rights and responsibilities. In the past, most adoptions were closed, meaning the birth mother did not maintain contact with the child or adoptive parents. Most adoptions now have some level of openness, allowing the birth mother to maintain a prearranged amount of contact with the child or adoptive parents. Adoption laws vary by state and can be complex. The U.S. Department of Health and Human Services offers comprehensive information for expectant parents who are considering adoption, including information on adoption laws by state, on the Child Welfare Information Gateway (https://www.childwelfare.gov/topics/adoption/).

Although adoption is not technically a medical matter, physicians may be asked to provide information, advice, or prenatal care. Several principles can assist family physicians in these cases. Assisting the patient in decision making and with coordination of care may require referrals to other professionals, such as social workers. Because of the potential for undue influence, physicians should not act as brokers for adoption, match prospective parents with mothers, or attempt to adopt the child of a patient they care for medically.[21] Hospital policies regarding adoption should be reviewed before labor begins. The primary responsibility of the physician is to the patient, not the adoptive parents. Previously, adopted infants were removed immediately after delivery. Women can now decide whether to hold the infant, breastfeed, or even care for the infant until discharge from the hospital.[21]

INDUCED ABORTION

Induced abortion is performed in the first or second trimester of pregnancy and involves either medical or surgical methods.[22] The first trimester is defined as up to 12 completed weeks of gestation, and the second trimester

Table 2. Advantages and Disadvantages of Induced Abortion

Abortion type	*Advantages*	*Disadvantages*
Medical	Available during early pregnancy Avoidance of anesthesia Avoidance of invasive procedure High success rate	Complications, although rare, may include infection, need for emergent surgery and blood transfusion, or retained products of conception More perceived bleeding Narcotics often needed for pain control Often requires patient follow-up Second-trimester abortion requires hospitalization Uncertain timing of completion
Surgical	Available during early pregnancy and in second trimester Control over timing of completion High success rate Less perceived bleeding No patient follow-up required in most cases	Invasive procedure More potential complications (e.g., cervical laceration, infection, hemorrhage, uterine perforation, retained products of conception) Usually requires anesthesia or local block

Adapted with permission from American College of Obstetricians and Gynecologists. Practice bulletin no. 143: medical management of first-trimester abortion. Obstet Gynecol. *2014;123(3):678.*

Table 3. First-Trimester Medical Abortion Regimens

Regimen	*Effectiveness*	*Evidence*
Mifepristone (Mifeprex), 600 mg orally, plus misoprostol (Cytotec), 400 mcg orally 48 hours later (FDA-approved regimen)	92% up to 49 days	n = 827; $P < .001$[25]
Mifepristone, 200 mg orally, plus misoprostol, 800 mcg vaginally, buccally, or sublingually 24 to 48 hours later	95% to 99% up to 63 days	Compared with FDA-approved regimen, RR = 1.07; 95% CI, 0.87 to 1.32[26,27]
Methotrexate, 50 mg per m^2 intramuscularly or 50 mg vaginally, plus misoprostol, 800 mcg vaginally three to seven days later	> 90% up to 49 days	No comparison with FDA-approved regimen; n = 394*[27]
Misoprostol, 800 mcg orally or vaginally every three hours for 12 hours	85% up to 49 days	Compared with FDA-approved regimen, RR = 2.50; 95% CI, 1.89 to 3.32[27]

CI = confidence interval; FDA = U.S. Food and Drug Administration; RR = relative risk.

**—Calculated by authors based on Cochrane review.[22]*

Information from references 22, and 25 through 27.

is defined as 13 to 26 weeks of gestation. The advantages and disadvantages of medical vs. surgical abortion are listed in *Table 2*.[23] Abortion laws, including how late in pregnancy an abortion can be performed, vary by state. A summary of these laws can be found at the Guttmacher Institute website (http://www.guttmacher.org/statecenter/spibs/spib_OAL.pdf).[24]

Most medically induced abortions occur in the first trimester, are uncomplicated, and can be managed by family physicians. First-trimester medical abortion generally involves the use of mifepristone (Mifeprex), a derivative of norethindrone that acts as a progesterone receptor antagonist, followed by misoprostol (Cytotec) up to 72 hours later. The regimen approved by the U.S. Food and Drug Administration (FDA) includes 600 mg of oral mifepristone, followed by 400 mcg of oral misoprostol. This regimen is 92% effective up to 49 days' gestation.[25] Complete abortion rates are higher with earlier gestations. Non–FDA-approved combinations that include 200 mg of oral mifepristone followed by 800 mcg of misoprostol given vaginally, buccally, or sublingually up to 72 hours later have an overall success rate of 95% to 99% up to 63 days' gestation.[26,27] Although the FDA-approved regimen and non–FDA-approved regimens have similar effectiveness (relative risk = 1.07; 95% CI, 0.87 to 1.32), the non–FDA-approved regimens are considered superior because of their reduced rate of adverse effects and lower cost.[23] Other less commonly used—and

less effective—medical abortion regimens include misoprostol only and methotrexate followed by misoprostol[27] *(Table 3[22,25-27])*. Infection after medical abortion is rare, and there is no strong evidence to support the universal use of prophylactic antibiotics. The mother's Rh status should be determined, and Rh_o(D) immune globulin (RhoGam) should be administered, if indicated.[23]

Vacuum aspiration and dilation and curettage are the most commonly used surgical methods for first-trimester pregnancy termination in the United States.[28] They are equally effective and have similar complication rates. Perioperative antibiotics prevent upper genital tract infections after surgical abortion.[29] Dilation of the cervix using osmotic dilators, prostaglandins, or mechanical methods is usually necessary before performing the aspiration or curettage component of the procedure. Vacuum aspiration is performed with a manual vacuum device or an electric vacuum aspirator.[28]

Medically induced abortion may be preferred in the second trimester if the woman wishes to avoid a surgical procedure and prefers to have an intact fetus. Multiple regimens exist *(Table 4)*.[30] Patients are usually admitted to the hospital because the duration of the abortion is variable and may result in more blood loss.[30]

Second-trimester surgical abortion involves the dilation and evacuation technique. Bilateral fetal upper and lower extremities, spine, and cranium must be accounted for after both medical and surgical abortion.[31]

Abdominal surgery such as hysterectomy or hysterotomy is rarely required for second-trimester abortion and is performed only if dilation and evacuation or medical abortion has failed or is contraindicated.[31]

Table 4. Second-Trimester Medical Abortion Regimens

Mifepristone (Mifeprex), 200 mg orally, followed in 24 to 48 hours by misoprostol (Cytotec), 400 mcg sublingually or buccally every three hours for up to five doses
Misoprostol, 400 mcg vaginally or sublingually every three hours for up to five doses
or
Loading dose of misoprostol, 600 to 800 mcg vaginally, may be used instead
Oxytocin (Pitocin), 20 to 100 units intravenously for three hours, followed by one hour without oxytocin for diuresis; may then slowly increase to 300 units over three hours

Information from reference 30.

Counseling Patients with Unintended Pregnancy

Women with unintended pregnancy may seek counseling from their family physician. Depending on the circumstances, this can be challenging. To assist our readers, this issue of *American Family Physician* also contains a Curbside Consultation (page 574) feature to offer more guidance on counseling techniques.

Data Sources: A PubMed search was completed in Clinical Queries using the key terms abortion and induced. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. PubMed searches were completed using the terms abortion, induced abortion, and adoption. Essential Evidence Plus, the National Guideline Clearinghouse, the Cochrane Database of Systematic Reviews, and bibliographies were also searched. Search dates: September 25, 2014, and January 30, 2015.

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Effects of Pressure to Abort on Women's Emotional Responses and Mental Health

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Abstract

Background

Women who feel pressured to agree to abortion are more likely to experience negative emotional and mental health reactions. But relatively little research has been conducted to explore the types and degree of pressures women face and their associated effects. Our study aims to investigate five types of pressure women may face and a sample of effects that may be associated with unwanted abortions.

Methods

A retrospective survey was distributed through a marketing research firm and completed by 1000 females aged 41 to 45, inclusive, living in the United States. The survey instrument included demographic questions and analog scales for respondents to rate the pressure to abort arising from male partners, family members, other persons, financial concerns, and other circumstances and 10 variables related to both positive and negative outcomes.

Results

Among 226 respondents who reported a history of abortion, perceived pressure to abort was significantly associated with more negative emotions; more disruption of daily life, work, or relationships; more frequent thoughts, dreams, or flashbacks to the abortion; more frequent feelings of loss, grief or sadness about the abortion; more moral and maternal conflict over the abortion decision; a decline in overall mental health that they attribute to their abortions; more desire or need for help to cope with negative feelings about the abortion. Overall, 61% reported high levels of pressure on at least one scale. Women with a history of abortion were four times more likely to quit the survey than women who did not have abortions, and those with a history of feeling pressured to abort also reported higher levels of stress related to completing the survey.

Discussion

Perceived pressures to choose abortion should be assessed before an abortion to better guide risk assessments, decision-making, and analyses of post-abortion adjustments in light of these risk factors. A history of abortion, especially when there was pressure to abort, is associated with more stress completing questionnaires touching on abortion experiences and with a higher dropout rate, a finding that is consistent with the view that abortion surveys are likely to underrepresent the experiences of the women who experience the most stress and negative reactions to their abortions. Abortion providers should screen for perceived pressures to abort and be prepared to offer counseling and services that will help women to avoid unwanted abortions.

Categories: Obstetrics/Gynecology, Psychology, Epidemiology/Public Health
Keywords: post-abortion mental health, post-abortion adjustments, health policy, pregnancy loss, unsafe abortions, reproductive rights, mental health, abortion

Introduction

The 2008 literature review by the American Psychological Association's Task Force on Mental Health and Abortion identified 15 risk factors for more negative mental health outcomes following abortion [1]. Among these is the "perceived pressure from others to terminate a pregnancy." Other reviews and studies have also identified pressure to choose abortion as a risk factor for greater difficulty in coping with the subsequent abortion [2-6]. Yet there is a great diversity in the types of pressures women self-report [7-10]. Pressure from male partners, parents, employers, health care providers, sex traffickers, and other persons may have varying degrees of effects on both the abortion decision and subsequent adjustments [10-13]. Similarly, pressure from situational factors, such as financial pressure, maternal health issues, fetal malformation, and other circumstances may also have varying degrees of effect on coping and satisfaction with abortion [14].

While all of the above-named pressures to undergo abortions are well-known, relatively little research has

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been done to differentiate these pressures and their separate and cumulative effects on post-abortion mental health. In this exploratory study, we seek to (a) confirm or disprove the association between pressures to abort and more negative post-abortion adjustments, and (b) begin the process of identifying which pressures have the greatest negative effects on post-abortion adjustments.

Materials And Methods

Study design and setting

This study is a retrospective survey of American women who completed an electronic survey form in October of 2022. The study design was approved by the Sterling Institutional Review Board (approval no. 10225). The survey instrument was developed in consultation with experts in abortion counseling and researchers who have published in the field of abortion's association with emotional and mental health effects. The survey included five statements regarding pressures to abort and 10 statements regarding outcome variables, collectively shown in Table *1*, along with the abbreviation for each pressure stated in this report. Respondents indicated their responses using a slider on a visual analog scale displayed on their own electronic devices. While no numbers were shown to the respondents when they slid their markers, their responses on the visual analog scale were automatically converted to the appropriate percentage in a range from 0 to 100.

Abbreviation	Complete statement or question	Scale of Agreement (0 to 100)
MalePr	I felt pressure to abort from my male partner.	Not at all | Very much so
FamilyPr	I felt pressure to abort from one or more family members.	Not at all | Very much so
OtherPr	I felt pressure to abort from someone else.	Not at all | Very much so
FinPr	I felt pressure to abort from financial concerns.	Not at all | Very much so
OtherCircPr	I felt pressure to abort from other circumstances.	Not at all | Very much so
PositiveEmotions	My positive emotions regarding the abortion are . . .	None at all | Very high
NegativeEmotions	My negative emotions regarding the abortion are . . .	None at all | Very high
InterferedwLife	Thoughts and feelings about my abortion have negatively interfered with daily life, work, or relationships.	Not at all true | Very true
NeededHelp	I have desired or needed help to better cope with negative feelings or behaviors due to my abortion.	Not at all true | Very true
IntrusiveThoughts	I have had frequent thoughts, dreams, or flashbacks to the abortion.	Not at all true | Very true
FrequentLoss	I have had frequent feelings of loss, grief, or sadness about the abortion.	Not at all true | Very true
BetterMentalHlth	Abortion made my mental health . . .	Very much worse | Very much better
SurveyStress	Completing this survey has increased feelings of stress.	Not at all true | Very true
MoralConflct	The idea of abortion conflicted with my moral beliefs.	Not at all | Very much so
MaternalConflict	The idea of abortion conflicted with my maternal desires.	Not at all | Very much so

TABLE 1: Survey questions and abbreviations

In brief, respondents rated the level of pressure, if any, they experienced from their male partner, their family, other persons, financial pressures, and other circumstances. To further our analyses, we also constructed the average score (AvgPr) and the maximum score (MaxPr) each woman reported across each of these five scales. The outcome scales rated each respondent's level of experience of positive emotions, negative emotions, disruption of normal life, desire for help to cope, intrusive thoughts, frequent feelings of loss, their assessment of abortion's impact on their mental health, and whether completing the survey increased feelings of stress.

Population

The surveyed population was drawn from 28 million Cint panelists in the United States [15]. Cint panelists are persons who voluntarily complete surveys using their own electronic devices in exchange for small rewards. Our selection criteria required Cint to obtain 1,000 completed surveys from females who are residents of the United States who were 41 to 45 years of age, inclusive, at a cost of three dollars per completed survey. This narrow age range was chosen to eliminate the confounding effects of age while

capturing the experience of women who have completed the majority of their reproductive lives.

Results

A total of 1161 persons identified by Cint to be females aged 41 to 45 answered at least the first page of our survey. The first two pages contained only demographic questions which were used to disqualify 122 respondents whose self-reported age or gender was outside our limits. Of the remaining 1039 qualified respondents, 39 failed to complete the survey, yielding a 96% completion rate. Of these qualified respondents, 248 women reported a history of abortion of whom 226 completed the full survey, for a completion rate of 91%. Women with a history of abortion were over four times (odds ratio (OR)=4.43, 95% confidence interval (CI)=2.31-8.49) more likely to drop out of the survey at or after the first question related to abortion compared to women who did not report a history of abortion and were routed to a different set of questions regarding their reproductive lives.

Demographic characteristics are shown in Table *2*. The first two columns allow a comparison of the U.S. census data for all persons over 18 years of age alongside the demographics for all 28 million U.S. residents in the Cint survey panels. The third column shows demographics provided by Cint for all women aged 41 to 45 in their survey panel. The fourth and fifth columns show the 1000 women who completed our survey, and the subset of 226 women who had abortions in our survey sample and report the demographics participants provided on the first page of our survey. The table reveals a reasonably good approximation of females in this age group relative to the national census data with four exceptions. First, U.S. census data shows that 11% of all residents over age 18 have not completed high school, whereas only 3% of the Cint panel of women 41 to 45 years of age have not completed high school. In large part, this may be due to the fact that middle-aged women have had more time to advance their education. In addition, less educated persons may be less inclined to agree to participate in survey panels. Second, our respondents somewhat underrepresent lower income groups, compared to both U.S. census data and all Cint panelists. Third, while the 226 women reporting a history of abortion in our panel are relatively similar to the entire Cint sample for women of this age group, national studies of abortion reveal that abortion rates among black women are three to four times higher than that of white women [16], a finding that is not reflected in our sample. Finally, our sample somewhat overrepresents women from the South U.S. census region.

	U.S. Census Data for All Persons	Cint U.S. Survey Panel for All Persons	Our Survey Sample (n=1000)	Our Abortion Subgroup (n=226)
Region				
Northeast	17	19	14	16
South	38	44	44	43
Midwest	21	19	21	19
West	24	18	21	22
Educational Attainment				
Less than high school graduate	11	4	4	1
High school graduate	26	27	33	35
University/Higher Education	49	54	46	49
Postgraduate Education	14	18	18	15
Household Income (2021)				
Under $25,000	17	23	13	12
$25,000-$49,999	19	17	15	14
$50,000-$79,999	19	24	26	28
$80,000-$99,999	9	11	19	19
Over $100,000	36	25	27	26
Ethnicity				
Asian	6	3	5	6
Black	14	13	15	14
Hispanic	19	12	14	15
White	59	68	59	57
Other	2	4	7	8

TABLE 2: Percentage of demographic characteristics in the United States census, Cint national panel, survey sample, and the subgroup of respondents who had abortions

All numbers are percentages for the associated demographic characteristic

The distributions for all the scales used are shown in Table *3*, including the means, standard deviation (SD), and quartiles. The quartiles for financial pressure, for example, show that 25% of respondents rated financial pressure as 15 or below, 50% (the median) rated this pressure as 63 or below, and 75% rated it as 85 or lower, with the last 25% rating it between 85 and 100. MaxPr shows over half of the women reporting at least one score above 91. Additional analyses of MaxPr revealed nearly one-third of the women (31.4%; 95% CI: 25.4% to 37.9%) rated at least one of the pressures at the extreme highest of the scale (100).

Abbreviation from Table 1	N	Mean	SD	Min	25%	Median	75%	Max
MalePr	226	31.3	35.4	0	0	12	63	100
FamilyPr	226	34.7	37.8	0	0	15	71	100
OtherPr	226	23.7	32.3	0	0	5.5	46	100
FinPr	226	54.6	36.6	0	15	63	85	100
OtherCircPr	226	64.7	33.5	0	47	73	98	100
MaxPr	226	80.3	25.7	0	69	91.5	100	100
AvgPr	226	41.8	21.9	0	27.8	40.1	56.8	100
PositiveEmotions	226	50.4	30.5	0	29	49	73	100
NegativeEmotions	226	50.7	33	0	23	51	78	100
InterferedwLife	226	35.7	33	0	3	30	59	100
NeededHelp	226	33.9	32.7	0	2	28	61	100
IntrusiveThoughts	226	33.2	33.6	0	1	22	60	100
FrequentLoss	226	39.3	34.5	0	3	35	67	100
BetterMentalHlth	226	49	23.4	0	35	50	61	100
SurveyStress	226	36.7	30.9	0	5	32.5	61	100
MoralConflict	226	49.1	34.8	0	19	50.5	76	100
MaternalConflict	226	46.3	35.1	0	9	50	76	100

TABLE 3: Descriptive statistics of the distribution of responses for pressure scales

The columns of this table represent for each question the number of respondents (N), the mean reported value, the standard deviation (SD), the minimum observed value (Min), the lower 25% quartile (25%), the median (50% quartile), the 75% percent quartile (75%), and the maximum (Max) observed value.

Figure *1* shows the percentage of respondents who reported little (<20), modest (21 to 40), moderate (41 to 60), substantial (61 to 80), and high (>80) levels of pressure for each pressure scale. For example, the MaxPr distribution using this scale revealed that 83.6% of women reported substantial to high levels of pressure on at least one scale.

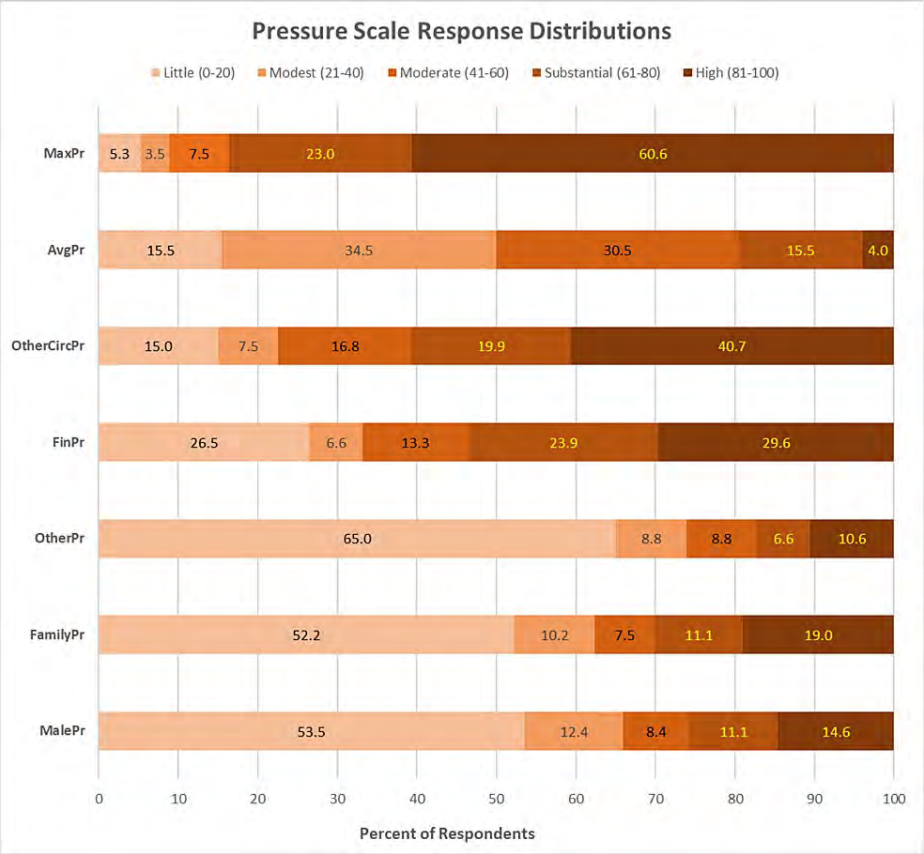

FIGURE 1: Pressure scale responses by the percentage of respondents grouped into five ranges

Abbreviation of pressures taken from Table 1.

Table *4* shows the correlations between our five pressure scales and 10 outcome scales. It reveals that the three interpersonal pressure scales (male partner, family, and other persons) are positively correlated to each other, indicating that many women report pressure from more than one other person. Feelings of pressure from financial concerns were mildly but significantly correlated to pressures from persons, but feelings of pressure from other circumstances were not. Notably, however, the mean score for pressure from other circumstances was the highest for all the means, yet at the same time this independent variable was the least strongly correlated to the outcome variables. By contrast, all three scales for pressure from other persons were significantly correlated with more negative outcomes on every outcome scale. Pressure from financial concerns was significantly correlated to worse outcomes for eight of the 10 outcome variables. Financial concerns were not correlated to intrusive thoughts or fewer positive feelings, though both might prove to be correlated with a larger sample size in light of the strongly skewed confidence intervals.

Variable	M	SD	MalePr	FamilyPr	OtherPr	FinPre	OtherCircPr
1. MalePr	31.33	35.36					
2. FamilyPr	34.67	37.75	.36** (.24, .47)				
3. OtherPr	23.74	32.28	.42** (.31, .52)	.53** (.43, .62)			
4. FinPr	54.62	36.58	.19** (.06, .31)	.15* (.02, .28)	.17** (.05, .30)		
5. OtherCircPr	64.68	33.53	0.02 (-.11, .15)	0.0 (-.13, .13)	0.1 (-.03, .23)	.40** (.29, .51)	
6. PositiveEmotions	50.37	30.54	-0.13 (-.26, .00)	-0.07 (-.20, .06)	-0.08 (-.21, .05)	-0.11 (-.24, .02)	0.06 (-.07, .19)
7. NegativeEmotions	50.65	32.97	.40** (.29, .51)	.34** (.21, .45)	.36** (.25, .47)	.32** (.20, .43)	.16* (.03, .28)
8. InterferedwLife	35.71	32.98	.40** (.28, .50)	.32** (.20, .44)	.45** (.34, .55)	.14* (.01, .26)	0.08 (-.05, .21)
9. NeededHelp	33.95	32.72	.42** (.30, .52)	.40** (.29, .51)	.48** (.37, .57)	.16* (.03, .28)	0.1 (-.03, .22)
10. IntrusiveThoughts	33.2	33.61	.46** (.35, .56)	.36** (.24, .47)	.54** (.44, .62)	0.1 (-.04, .22)	0.12 (-.01, .25)
11. FrequentLoss	39.3	34.49	.41** (.30, .51)	.39** (.27, .50)	.46** (.35, .56)	.17* (.04, .29)	.15* (.02, .28)
12. BetterMentalHlth	49.03	23.37	-.17** (-.30, -.04)	-.19** (-.31, -.06)	-0.13 (-.25, .00)	-0.02 (-.15, .11)	-0.01 (-.14, .12)
13. SurveyStress	36.72	30.93	.42** (.30, .52)	.28** (.15, .39)	.28** (.16, .40)	.14* (.01, .27)	0.06 (-.07, .19)
14. MoralConflict	49.11	34.79	.40** (.29, .51)	.31** (.19, .42)	.40** (.29, .51)	.21** (.08, .33)	0.11 (-.02, .24)
15. MaternalConflict	46.32	35.08	.40** (.28, .50)	.32** (.20, .44)	.39** (.28, .50)	.24** (.11, .36)	0.11 (-.02, .23)

TABLE 4: Correlation matrix of pressure scales and outcome scales

The mean (M) and standard deviations (SD) are shown for each variable. Correlations between variables are shown along with the range in parentheses which shows the 95% confidence interval for each correlation. * indicates p < .05. ** indicates p < .01.

Correlations with the two constructed pressure scales, MaxPr and AvgPr, are shown in Table *5*, along with correlations between each of the dependent variables. These results revealed that AvgPr provided a better correlation to outcome variables than MaxPr. In addition, negative outcomes generally showed moderate to strong correlations with each other, indicating that women who experienced one negative mental health outcome were more likely to experience negative outcomes across several domains.

Variable	M	SD	1	2	3	4	5	6	7	8	9	10	11
1. AvgPr	41.81	21.89											
2. MaxPr	80.28	25.65	.55** (.46, .64)										
3. PositiveEmotions	50.37	30.54	-0.11 (-.23, .02)	-0.11 (-.24, .02)									
4. NegativeEmotions	50.65	32.97	.51** (.41, .60)	.29** (.17, .41)	-.53** (-.62, -.43)								
5. InterferedwLife	35.71	32.98	.44** (.33, .54)	.15* (.02, .27)	-.35** (-.46, -.23)	.62** (.53, .70)							
6. NeededHelp	33.95	32.72	.50** (.39, .59)	.19** (.07, .32)	-.31** (-.43, -.19)	.59** (.50, .67)	.84** (.79, .87)						
7. IntrusiveThoughts	33.2	33.61	.50** (.40, .59)	.26** (.14, .38)	-.30** (-.41, -.18)	.56** (.46, .64)	.68** (.60, .74)	.71** (.64, .77)					
8. FrequentLoss	39.3	34.49	.51** (.40, .60)	.30** (.17, .41)	-.29** (-.40, -.16)	.59** (.49, .66)	.67** (.59, .74)	.69** (.61, .75)	.80** (.75, .85)				
9. BetterMentalHlth	49.03	23.37	-.17* (-.29, -.04)	-.15* (-.27, -.02)	.56** (.47, .65)	-.47** (-.57, -.36)	-.45** (-.55, -.34)	-.43** (-.53, -.31)	-.39** (-.50, -.27)	-.47** (-.56, -.36)			
10. SurveyStress	36.72	30.93	.38** (.26, .49)	.16* (.03, .29)	-.37** (-.47, -.25)	.55** (.45, .63)	.58** (.49, .66)	.53** (.43, .62)	.54** (.44, .63)	.54** (.44, .63)	-.32** (-.43, -.20)		
11. MoralConflict	49.11	34.79	.46** (.35, .56)	.24** (.11, .36)	-.32** (-.44, -.20)	.67** (.59, .73)	.61** (.52, .69)	.57** (.48, .65)	.48** (.37, .58)	.58** (.48, .66)	-.30** (-.41, -.17)	.47** (.36, .57)	
12. MaternalConflict	46.32	35.08	.47** (.36, .56)	.22** (.09, .34)	-.29** (-.41, -.17)	.64** (.55, .71)	.61** (.52, .68)	.52** (.42, .61)	.48** (.37, .57)	.61** (.52, .69)	-.33** (-.44, -.20)	.41** (.29, .51)	.70** (.62, .76)

TABLE 5: Correlations between the constructed pressure scales and the outcome scales

The mean (M) and standard deviations (SD) are shown for each variable. Correlations between variables are shown along with the range in parentheses which shows the 95% confidence interval for each correlation. * indicates p < .05. ** indicates p < .01.

Discussion

Our findings confirmed that women who perceived pressure to abort, especially from their male partners, families, or other persons, are more likely to report more negative reactions to abortion. Those experiencing pressure reported more negative emotions; more disruption of daily life, work, or relationships; more frequent thoughts, dreams, or flashbacks to the abortion; more frequent feelings of loss, grief, or sadness about the abortion; more moral and maternal conflict over the abortion decision; a decline in overall mental health that they attribute to their abortions; and more desire or need for help to cope with negative feelings about the abortion. In addition, women who reported feeling more pressure to choose abortion also reported higher levels of stress completing the survey. This last finding is consistent with previous studies suggesting that questionnaire-based studies of abortion and mental health are likely to underreport negative reactions due to self-censure bias [3].

In our sample, 61% of the women reported experiencing a high level of pressure to abort on at least one scale. However, the scale with the highest mean score was for pressure to abort from other circumstances, OtherCircPr, which was the one scale that was also the least correlated to any of the outcome scales. Given that this open-ended category had the highest average intensity, it suggests that there are a number of additional types of pressure that are most important in the abortion decision of many women. Future research efforts should incorporate more detailed scales examining all the many reasons why women choose abortion, including health concerns for themselves or for fetal malformation, having already reached their family size goals, instability in the relationship with the male partner, and conflicts with short-term and/or long-term life goals, for example [17].

In addition, we found that women with a history of abortion were more likely to drop out of the survey once the topic of abortion was raised. Among those who completed the survey, those who reported feeling pressured to abort experienced more stress completing the survey than those who faced little or no pressure

to abort. These findings underscore the fact that every survey of women's abortion experiences is likely to suffer from selection bias, with women who feel the most pressure to abort and who are most likely to have negative reactions being least likely to participate in or complete follow-up surveys.

It is unclear how well our survey sample reflects the national population of all women who have had an abortion. Our sample is clearly limited to residents in the United States and our age range of women aged 41 to 45 years. Moreover, the demographic characteristics shown in Table *2* suggest our findings may underrepresent lower-income and lower-educated women and some minority groups, at least in comparison to nationally reported abortion rates. Therefore, caution should be exercised in drawing any conclusions regarding the actual frequency of women feeling pressured to abort in the general population. On the other hand, it is highly likely that the correlations between the types of pressures identified, and the negative outcome variables utilized in our study, do apply to the general population of women who have experienced abortion. In that regard, our study shows that it is important for future studies on emotional responses to abortion to include questions rating the level of pressures women face, particularly from other people, prior to undergoing their abortions, as these pressures are clearly important risk factors for more negative outcomes.

Another weakness in our study is that the 10 outcome scales utilized in our survey were entirely self-assessments. We have no data on psychiatric diagnoses nor did we use any psychometric scales. The latter was not employed since these would have vastly lengthened the survey, depressed response rates and to the degree that they are often limited to feelings within the last week or 30 days, and may have failed to represent the "entire history" of women's post-abortion adjustments. In that regard, while we would encourage the use of psychometric scales in future investigations, we believe the 10 self-assessment scales used in the present study provide an important contribution to our understanding of how various pressures to abort impact different aspects of post-abortion adjustments.

An additional weakness is that our data is based entirely on retrospective ratings. Memories of past events may be colored by years of reflection, subsequent experiences, and reaction formation. Clearly, it would be better to gather information about the types and degrees of pressures women face to have an abortion during the counseling period prior to an abortion. Identification of these risk factors would provide an opportunity for better counseling and discussion of these pressures and their associated risks. It would also provide better data for correlation to post-abortion adjustment data collected in subsequent case series investigations.

Conclusions

Women frequently choose abortion due to perceived pressures from other people, financial concerns, or other circumstantial pressures. These pressures, individually and/or together, are strongly associated with more negative emotions about their abortion; more disruptions of their daily life, work, or relationships; more frequent dreams, flashbacks, or intrusive thoughts about their abortions; more frequent feelings of loss, grief, or sadness about their abortions; more moral and maternal conflict over their abortion decisions; a perceived decline in their overall mental health that they attribute to their abortions; and a higher degree of desire or need for help to cope with negative feelings about their abortions.

Additional research is needed to better identify the types of pressures women face and the variety of outcomes associated with each type of pressure. Abortion providers should screen for perceived pressures to abort and should counsel women accordingly. Therapists and counselors offering care to those struggling with post-abortion emotional adjustments or mental health issues should also assess perceived pressures to abort.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Sterling Institutional Review Board issued approval 10225. Sterling Institutional Review Board determined that this survey-based study is exempt from IRB review pursuant to the terms of the U.S. Department of Health and Human Service's Policy for Protection of Human Research Subjects at 45 C.F.R. §46.104(d). . **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** David C. Reardon declare(s) personal fees from Charlotte Lozier Institute. David C. Reardon declare(s) employment from Elliot Institute. Tessa Longbons declare(s) employment from Charlotte Lozier Institute. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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The Effects of Abortion Decision Rightness and Decision Type on Women's Satisfaction and Mental Health

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Abstract

Background

A case series report based on the Turnaway Study has previously concluded that 99% of women with a history of abortion will continue to affirm satisfaction with their decisions to abort. Those findings have been called into question due to a low participation rate (31%) and reliance on a single yes/no assessment of decision satisfaction.

Aim

To utilize more sensitive scales in assessing decision satisfaction and the associated mental health outcomes women attribute to their abortions.

Method

A retrospective survey was completed by 1,000 females, aged 41-45, living in the United States. The survey instrument included 11 visual analog scales for respondents to rate their personal preferences and outcomes they attributed to their abortion decisions. A categorical question allowed women to identify if their abortions were wanted and consistent with their own values and preferences, inconsistent with their values and preferences, unwanted, or coerced. Linear regression models were tested to identify which of three decision scales best predicted positive or negative emotions, effects on mental health, emotional attachment, personal preferences, moral conflict, and other factors relevant to an assessment of satisfaction with a decision to abort.

Results

Of 226 women reporting a history of abortion, 33% identified it as wanted, 43% as accepted but inconsistent with their values and preferences, and 24% as unwanted or coerced. Only wanted abortions were associated with positive emotions or mental health gains. All other groups attributed more negative emotions and mental health outcomes to their abortions. Sixty percent reported they would have preferred to give birth if they had received more support from others or had more financial security.

Conclusions

Perceived pressure to abort is strongly associated with women attributing more negative mental health outcomes to their abortions. The one-third of women for whom abortion is wanted and consistent with their values and preferences are most likely over-represented in studies initiated at abortion clinics. More research is needed to understand better the experience of the two-thirds of women for whom abortion is unwanted, coerced, or otherwise inconsistent with their own values and preferences.

Categories: Obstetrics/Gynecology, Psychology, Public Health
Keywords: coerced abortion, unwanted abortion, abortion, mental health, reproductive rights, unsafe abortions, pregnancy loss, health policy, post-abortion adjustments, post-abortion mental health

Introduction

A 2015 study undertaken by an abortion advocacy group, Advancing New Standards in Reproductive Health (ANSIRH), reported that 99% of women who had undergone abortion three years earlier answered yes to the question: "Given your situation, was the decision to have an abortion the right decision for you?" [1,2]. These findings were interpreted by ANSIRH as evidence of nearly universal "satisfaction with the abortion decision" and widely reported by mass media outlets as evidence that women seldom experience regrets or mental health issues following abortion [3]. But in a separate analysis of the same sample of women, ANSIRH elsewhere reported high levels of regret (41-66%), sadness (64-74%), guilt (53-63%) and anger (31-43%) [4]. This incongruency between high rates of negative feelings and the reported 99% "decision

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satisfaction," as the findings were described by the authors, invited considerable criticism of both ANSIRH's methodology and their sample's representativeness [1,3,5,6]. Concerns over the accuracy and interpretation of these results were further heightened by ANSIRH's refusal to share their research instruments for review or their data for reanalysis [5].

A chief methodological criticism was that ANSIRH's binary yes/no question lacked a scale for identifying the degree of "decision satisfaction" [3]. In addition, the question preface ("Given your situation") may have fixated responses on beliefs and feelings at the time of the abortion. Aside from the risk of inviting reaction formation, a response of "yes" to the ANSIRH question may have meant nothing more than an affirmation that respondents tried to make the "right decision" given their situation at that time. In such cases, it would not actually inform us if women believed their abortions improved their lives, much less if their experience was free of any regrets, guilt, nightmares, depression, suicidal thoughts, substance use, rapid repeat pregnancy, or any other negative effects which research has shown to be associated with abortion [5,7-10].

Another major criticism of ANSIRH's decision rightness analyses relied on their use of a non-representative sample of women in their longitudinal case series branded as the Turnaway Study [3]. The invitations to participate were non-random. Moreover, only 31% of the women invited to participate in the ANSIRH survey completed at least one interview and half of that fraction dropped out prior to the last interview [3,11]. The poor participation rate is further highlighted in contrast to another ANSIRH study for which 72% of women seeking an abortion participated, though notably this latter study only requested women to complete a pre-abortion questionnaire; therefore, invitees did not face any anticipation of anxieties regarding an interview to discuss their post-abortion feelings [12]. It seems likely that the low 31% participation rate in ANSIRH's decision rightness sample reflects a high degree of selection bias. This conclusion is consistent with the findings of studies that have found that women who anticipate the most negative reactions to their abortions are least likely to agree to participate in follow-up interviews when invited to do so at an abortion clinic [5,13,14]. Moreover, in a previous analysis of the present retrospective survey, we reported a 91% completion rate among women who had abortions after the topic of abortion was revealed [15]. This closely matches the 92% participation rate of a study regarding emotional adjustments following prophylactic mastectomies [16]. This suggests that retrospective studies initiated after an abortion has been completed, and not in association with the abortion clinic itself, may provoke less stress and therefore higher participation rates.

While ANSIRH's effort to invite women to offer a post hoc evaluation of the "rightness" of their abortion decision is not without merit, answers to this question should have been evaluated in the context of other measures of benefits or harm women attribute to their abortion experience. This is important because many studies have revealed that negative and positive reactions frequently co-exist [5]. While that fact was recognized in ANSIRH's own analyses, they concluded that decision rightness and emotional adjustment are not significantly correlated, writing "Believing abortion was the wrong decision and experiencing negative emotions are distinct…,", a conclusion that is at odds with our own research and the self-reports of women [1,5].

In addition, ANSIRH's researchers and other proponents of unrestricted abortion generally analyze and interpret their findings from the perspective that women only seek abortion for "unwanted pregnancies" despite consistent evidence that a substantial percentage of women are aborting pregnancies that were planned or welcomed, often due to pressure to abort from others or circumstances [5,15,17-19]. For example, analyses of the National Longitudinal Survey of Adolescent to Adult Health revealed that approximately 20% of women admitting a history of abortion reported that one or more of their aborted pregnancies had been wanted [20]. In addition, the same study found that abortion of wanted pregnancies was significantly associated with higher rates of subsequent psychological disorders. Those findings are consistent with the American Psychological Association's 2008 task force report which found that negative reactions to abortion were more common for women "terminating a pregnancy that is wanted or meaningful" or when there is "perceived pressure from others" [5,21].

In light of the above issues, the goal of the present study is to improve on the assessment and understanding of decision rightness, decision types, and decision satisfaction utilizing more nuanced scales and a more random and representative sample of women than was utilized in ANSIRH's Turnaway Study. An additional goal is to understand how assessments of decision rightness correlate to other measures applicable to assessing decision satisfaction and the mental health adjustments associated with abortion. Regarding these other measures, we hypothesized that differences in the abortion decision scale and a related decision type scale would be strongly correlated with the degree of self-reported moral and/or maternal conflicts, positive and/or negative emotional reactions, and the direction of mental health effects that women self-attribute to their abortions.

Materials And Methods

Experts in abortion and mental health research were consulted in preparing a questionnaire for our Unwanted Abortion Studies, a series of investigations into the prevalence and effects of abortions that conflict with women's own maternal preferences and moral beliefs. Employing the survey panel services of Cint.com, we collected 1,000 completed surveys from females who are residents of the US and 41 to 45

years of age, both inclusive. Cint panelists are persons who voluntarily complete surveys using their own electronic devices in exchange for small rewards with a value under $3. The Cint survey panels include over 28 million US residents. A narrow age range was chosen to eliminate the confounding effects of age while capturing the experience of women who have completed the majority of their reproductive lives. Additional details about the sample were previously published in an analysis of pressures to choose abortion [15]. Notably, in that previous study, we found that the demographic characteristics of the subgroup of women who reported abortions may somewhat underrepresent women who are less educated, less affluent, and Black, compared to the distribution rates reported elsewhere for women in these subgroups [15,22,23].

The questionnaire included 11 visual analog scales shown in Table *1*. For each scale respondents were shown a horizontal line with a slider they moved to show the range of their agreement or disagreement relative to the two labels at either end. Responses were electronically coded from zero to 100, resulting in a scale range of 101 points. Among these items, ANSIRH's central research question was reframed as the statement, "Given my situation, the decision to have an abortion was the right decision for me." This allowed respondents to provide a range of agreement from "Not at all" to "Very much so," rather than simply yes or no.

Abbreviation	Complete statement or question	Scale of Agreement
RightDecision	Given my situation, the decision to have an abortion was the right decision for me.	Not at all true | Very true
PersonalPref	Excluding the pressures I faced to have an abortion, in terms of satisfying my own personal preferences the abortion was . . .	Very unwanted | Very wanted
MoreSupport	If I had received more support from others, I would have continued the pregnancy.	Not at all true | Very true
MoreFinSecurity	If I had more financial security, I would have continued the pregnancy.	Not at all true | Very true
MoralConflict	The idea of abortion conflicted with my maternal desires.	Not at all | Very much so
MaternalConflict	The idea of abortion conflicted with my moral beliefs.	Not at all | Very much so
EmotionalAttachment	My emotional attachment to the pregnancy was...	None at all | Very high
HumanLife	I perceive the pregnancy as being . . .	A clump of cells | A human life
PositiveEmotions	My positive emotions regarding the abortion are . . .	None at all | Very high
NegativeEmotions	My negative emotions regarding the abortion are . . .	None at all | Very high
BetterMentalHlth	Abortion made my mental health . . .	Very much worse | Very much better

TABLE 1: Survey Scales, abbreviations and range labels (0 to 100)

An additional categorical question was asked: "Which best describes your abortion decision?" Respondents were presented with four possible answers: "Wanted and consistent with my values and preferences," (Wanted), "Accepted but inconsistent with my values or preferences" (Inconsistent), "Unwanted and contrary to my values and preferences" (Unwanted) or "Coerced and contrary to my values and preferences" (Coerced). For parametric analyses, these categorical responses were recoded from 1 through 4 from Wanted, Inconsistent, Unwanted, and Coerced, respectively.

Three additional variables were calculated for this analysis. The first was an assessment of the more dominant trend in their emotional response to their abortions (NetEmotions), calculated by subtracting the score for NegativeEmotions from PositiveEmotions, yielding a possible range from -100 to +100. BetterMentalHlth was recoded using the formula 2*(BetterMentalHlth-50), yielding a range from -100 to +100, and assigned to a variable for mental health effects (MHeffects) with the sign and value representing both the direction (negative or positive) and degree of the effect women attributed to their abortions. Third, we recoded RightDecision scores below and above 50 to RightD2 as a zero or one, respectively, in order to approximate the equivalent of a no or yes answer to ANSIRH's original question.

Finally, three univariate linear regression models, separately utilizing RightDecision, RightD2, and DecisionType as independent variables, were run for each of the dependent variables and were tested for best fit using Akaike information criterion (AIC).

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by Sterling Institutional Review Board issued (ID:10225). Consent for survey participation, without prior notice of the

topic, was digitally obtained from all respondents by Cint.com. No information was collected that would allow the authors to identify individual participants. Analyses were conducted using RStudio (Build 576; Posit, Boston, MA).

Results

To obtain a total of 1,000 completed surveys, a total of 1,161 persons identified by Cint to be females in our age range responded to a survey invitation that did not reveal the topic. The first two pages contained only demographic questions which were used to disqualify 122 respondents based on their self-reported age or gender. Of the remaining 1,039 respondents, 248 (23.7%) reported a history of abortion, which closely matches the Guttmacher Institute's estimate that by the age of 45, 23.7% of American women will experience an induced abortion [22]. Of the 248 reporting a history of abortion, 226 (91%) completed the survey. Only the latter were included in the analyses.

Regarding DecisionType, 33% described their abortions as Wanted, 43% as Inconsistent, 14% as Unwanted and 10% as Coerced. In addition, 54% answered mostly affirmative (≥50) to the statement that they would have continued their pregnancy if they had more financial security, 42% would have given birth if they had more support from others, and 60% reported they would have preferred to give birth if they had received either more emotional support or had more financial security.

General descriptive statistics for scales, including the mean (M), standard deviation (SD), quartiles and the minimum and maximum responses are shown in Table *2*. This table reveals that even while the mean of the RightDecision scale (75.55) was well above the centerpoint (50) the mean of all the other variables were either near the center or were negative.

Label	M	SD	min	25%	median	75%	max
RightDecision	75.55	27.79	0	59	84	100	100
PersonalPref	54.46	31.97	0	33	52	80	100
MoreSupport	41.30	35.69	0	3	37	74	100
MoreFinSecurity	48.52	37.45	0	4	54	83	100
MoralConflict	49.11	34.79	0	19	51	76	100
MaternalConflict	46.32	35.08	0	9	50	76	100
EmotionalAttachment	48.81	31.63	0	21	49	76	100
HumanLife	52.55	34.55	0	20	51	83	100
PositiveEmotions	50.37	30.54	0	29	49	73	100
NegativeEmotions	50.65	32.97	0	23	51	78	100
NetEmotions	-0.28	55.65	-100	-39	0	36	100
BetterMentalHlth	49.03	23.37	0	35	50	61	100
MHeffect	-1.94	46.74	-100	-30	0	22	100

TABLE 2: Descriptive statistics of variables

Descriptive statistics of variables, including mean (M), standard deviation (SD), and quartiles

Figure *1* shows the mean score for each scale segregated by the self-identified decision type groups: Wanted, Inconsistent, Unwanted, Coerced. In each case, the results revealed a consistent trend. Women whose abortions were wanted and consistent with their values and preferences reported the highest average score for RightDecision, PersonalPref, NetEmotions, and MHeffect. The three other groups were all more likely to attribute an overall negative effect on their mental health to their abortions, more negative than positive feelings, more moral and maternal conflicts over their abortion decision, less confidence in the rightness of their decision, less satisfaction with their decision as aligning with their own personal preferences, and were more likely to report that they would have given birth if they had received more support from others and/or had more financial security.

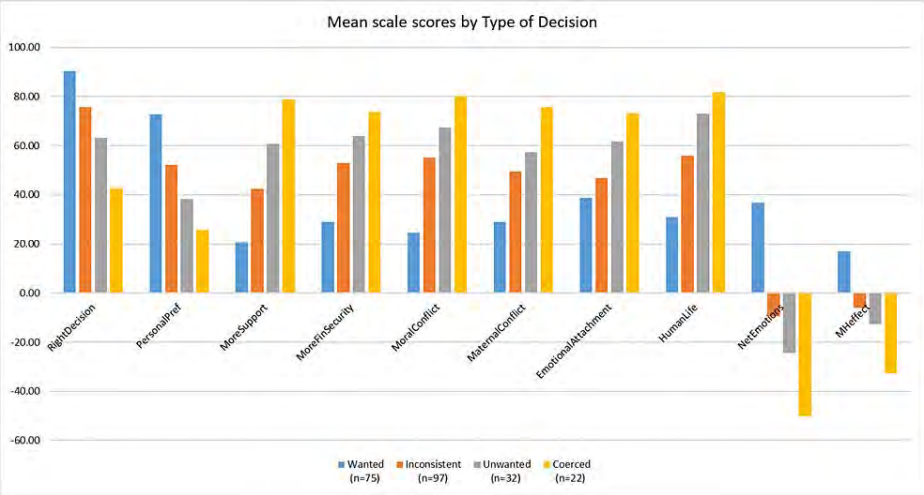

FIGURE 1: Mean scale scores disaggregated by DecisionType

The image was created by the authors using Microsoft Excel.

Table *3* shows the exact values for each data point shown in Figure *1*, plus the additional variable, RightD2 which approximates the distribution of “yes” or “no” to the ANSIRH decision rightness question. RightD2 indicates that 94.7%, 89.7%, 62.5%, and 40.9% for the Wanted, Inconsistent, Unwanted, and Coerced groups, respectively, would most have answered “yes” if asked ANSIRH’s form of the question.

	Wanted (n=75)	Inconsistent (n=97)	Unwanted (n=32)	Coerced (n=22)	Total (n=226)
RightD2	0.9466	0.8969	0.6250	0.4090	0.8274
RightDecision	90.25	75.70	63.22	42.68	75.55
PersonalPref	72.72	52.23	38.16	25.82	54.46
MoreSupport	20.57	42.35	60.88	78.82	41.30
MoreFinSecurity	28.88	52.91	64.00	73.64	48.52
MoralConflict	24.63	55.03	67.28	80.00	49.11
MaternalConflict	28.88	49.52	57.28	75.73	46.32
EmotionalAttachment	38.64	46.88	61.72	73.23	48.81
HumanLife	30.93	55.90	72.91	81.91	52.55
NetEmotions	36.69	-9.60	-24.38	-50.23	-0.28
MHeffect	16.91	-5.98	-12.63	-32.82	-1.94

TABLE 3: Mean scale scores by DecisionType groups

Table *4* shows the correlation coefficients for every combination of the variables and reveals that all of these variables were significantly correlated to each other with p<.01 for all cases. The strongest correlation (.70) was between MaternalConflict and MoralConflict. There was also a strong correlation (.68) between MoreFinSecurity and MoreSupport, which suggests that in many cases the lack of support from others was linked to a perception that the other persons argued for the abortion due to financial considerations. The next strongest correlation (.65) was between EmotionalAttachment to the unborn child and MaternalConflict, which was also mirrored in a high correlation (.57) between the perception that the pregnancy involved a HumanLife and EmotionalAttachment.

Variable	1	2	3	4	5	6	7	8	9	10
1. TypeDecision										
2. RightDecision	-.51**									
	[-.60, -.40]									
3. PersonalPref	-.47**	.44**								
	[-.57, -.36]	[.32, .54]								
4. MoreSupport	.51**	-.47**	-.36**							
	[.41, .60]	[-.57, -.36]	[-.47, -.24]							
5. MoreFinSecurity	.39**	-.34**	-.30**	.68**						
	[.28, .50]	[-.45, -.22]	[-.41, -.17]	[.60, .74]						
6. MoralConflict	.52**	-.39**	-.30**	.58**	.45**					
	[.42, .61]	[-.49, -.27]	[-.42, -.18]	[.49, .66]	[.34, .55]					
7. MaternalConflict	.40**	-.36**	-.39**	.54**	.44**	.70**				
	[.29, .51]	[-.47, -.25]	[-.50, -.28]	[.44, .63]	[.33, .54]	[.62, .76]				
8. EmotionalAttachment	.34**	-.39**	-.40**	.49**	.35**	.50**	.65**			
	[.22, .45]	[-.50, -.28]	[-.50, -.28]	[.39, .58]	[.23, .46]	[.39, .59]	[.57, .72]			
9. HumanLife	.49**	-.39**	-.41**	.55**	.37**	.54**	.52**	.57**		
	[.39, .59]	[-.49, -.27]	[-.51, -.29]	[.45, .64]	[.25, .48]	[.44, .63]	[.42, .61]	[.48, .65]		
10. NetEmotions	-.49**	.50**	.53**	-.48**	-.55**	-.57**	-.54**	-.42**	-.47**	
	[-.59, -.39]	[.40, .59]	[.43, .62]	[-.58, -.37]	[-.63, -.45]	[-.65, -.48]	[-.62, -.44]	[-.52, -.31]	[-.57, -.36]	
11. MHeffect	-.32**	.43**	.40**	-.27**	-.28**	-.30**	-.33**	-.36**	-.38**	.59**
	[-.43, -.20]	[.32, .53]	[.28, .50]	[-.38, -.14]	[-.40, -.16]	[-.41, -.17]	[-.44, -.20]	[-.46, -.24]	[-.49, -.27]	[.50, .67]

TABLE 4: Correlation matrix of all variables with confidence intervals

Values in square brackets indicate the 95% confidence interval for each correlation. The confidence interval is a plausible range of population correlations that could have caused the sample correlation.

* indicates p < .05; ** indicates p < .01

For each outcome variable, three univariate linear regression models were constructed using DecisionType, RightDecision, and RightD2 as separate independent variables. AIC model selection was then used to identify which independent variable was the best-fit model for each outcome variable. RightD2, emulating ANSIRH's binary variable, had the worst fit for every model tested. RightDecision had the best fit for three outcome variables: EmotionalAttachment, NetEmotions, and MHeffect. DecisionType was the best fit for all other outcome variables.

Discussion

Our findings revealed that only one in three women described their abortions as both wanted and consistent with their own values and preferences. Two-thirds experienced their abortion decision as a violation of their own values and preferences, with 24% describing their abortions as unwanted or coerced. A majority of women who had abortions (60%) reported they would have carried to term if they had received more support from others and/or had more financial security. Both factors indicate that abortion is a marginal, or even unwanted, choice for most women. These findings are consistent with the results of other investigations reporting high rates of perceived pressure to abort and ambivalence regarding abortion decisions [24-28].

Overall, only women who describe their abortion choice as wanted and consistent with their own values and preferences attributed any mental health benefits or a net gain in positive emotions to their abortions. All

other groups attributed more negative emotions and a decline in mental health to their abortions. For these other groups, more social support, both from individuals and society, especially in terms of financial assistance, might empower those women who are at greatest risk of unwanted abortions to make choices more in line with their own personal values and preferences.

ANSIRH's studies predicted that 99% of women with a history of abortion would affirm that, given their individual situations, abortion was the right choice [1]. In our sample, however, when the RightDecision scale was converted to a binary RightD2 (simulating ANSIRH's binary yes or no decision assessment) only 82.7% mostly agreed with the statement that abortion was the right decision.

Greater insight is obtained, however, when RightDecision is segregated by our DecisionType variable. That segregation reveals that the Wanted group, for whom the abortion choice was consistent with their own values and preferences, was most similar to ANSIRH's sample, with 94.7% agreeing (RightDecision≥50) that their decision was the right decision.

The observed disparity between ANSIRH's sample and our own are most likely due to ANSIRH's methodology. Previous studies have shown that women who anticipate negative feelings about their abortions are least likely to accept requests at abortion clinics for follow-up interviews [5,13,29]. This results in self-censure, with the women who are most prone to negative outcomes declining to participate. ANSIRH's selection bias was further exacerbated by a non-random invitation process, which included total exclusion of women seeking abortions due to suspected fetal anomaly, a subgroup known to be at higher risk of more negative reactions [2,5]. Even with the incentive of a $50 gift card for each interview, only 31% of the women invited to participate in ANSIRH's post-abortion survey completed at least one interview.

By comparison, our retrospective survey through Cint.com panels had a 91% completion rate with a cost of only $3 per completed interview [15]. Notably, in a pre-abortion survey conducted by ANSIRH, 70% of women asked to participate completed the in-clinic survey [12]. This is over double the participation rate of their post-abortion survey, the Turnaway Study. This higher participation rate was most likely possible because abortion patients were not asked to participate in a post-abortion study, which many likely perceived as a more stressful experience. This difference suggests that abortion clinic-initiated studies might obtain more representative samples of patients when post-abortion interviews are not required. It is likely that retrospective studies that are not connected with the abortion provider, such as ours, are associated with less stress and avoidance behaviors, especially for women who are being anonymously queried many years after their abortion experiences.

In short, our findings suggest that clinic-initiated surveys are likely to oversample women for whom the abortion decision is wanted and consistent with their own values and preferences and are likely to underrepresent, or even miss altogether, women for whom the abortion is unwanted or coerced, since the latter may be least likely to agree to follow-up interviews. Notably, the 31% participation rate in ANSIRH's Turnaway Study closely parallels the 33% of women in our sample who described their abortions as wanted and consistent with their values and preferences. In addition, our findings contradict ANSIRH's hypothesis that decision satisfaction and emotional responses are not linked [1].

Another key finding of our study is that ANSIRH's binary "decision rightness" question is clearly not representative of decision satisfaction. The majority of women in our sample who reported agreement (≥50) with the statement "Given my situation, the decision to have an abortion was the right decision for me," elsewhere indicated a preference for having given birth rather than having an abortion. This is especially clear in the responses related to DecisionType, MoreSupport, and MoreFinSecurity. At least in part, the predicate phrase, "given my situation" in the ANSIRH question may have led many women to interpret the statement as equivalent to "I made the best decision I could at that time." An affirmation of having made the best decision available to oneself does not imply, much less promise, satisfaction with that decision. In addition, even the phrase "right decision" invites ambiguity, both for respondents and the interpreters of these results. Was the decision "right" because it was the preferred choice, their most beneficial choice, the only available or even allowed choice (in cases of coercion and abuse), the right moral choice, a civil right, or merely "right" because the question triggers a reaction formation response leaning toward an affirmation of a past choice that cannot be changed? Future research should investigate each of these options, all of which reveal important nuances in women's abortion choices and their retrospective evaluation of those choices.

In general, our findings reveal that DecisionType provides a better metric for gauging issues related to satisfaction or dissatisfaction with an abortion decision than RightD2, which was most similar to ANSIRH's dichotomous measure. But our RightDecision scale provided a better linear regression fit than DecisionType for the variables EmotionalAttachment, NetEmotions, and MHeffect. This may be true because the 101-point RightDecision scale allowed for more sensitivity than our four categories for DecisionType. The latter might be improved by implementation on an analog sliding scale. Further study is necessary to determine if any single question regarding the abortion decision can provide the best model fit for predicting the relative benefits and risks that specific women are most likely to experience, given their own unique situations. Enough is already known to inform pre-abortion screening and counseling services in order to better counsel women who are at greatest risk of unwanted and unsafe abortions [30], but a greater focus on

these issues is warranted both in research and clinical settings.

One strength of our study is that the total percentage of respondents reporting a history of abortion closely matches the expected rate for this age group [22]. In addition, compared to ANSIRH's 31% completion rate of their first interview, our 91% completion rate for women reporting a history of abortion was very high. However, that 9% drop-out rate was still four times higher than that that of women without a history of abortion, suggesting that self-censure is likely to continue to bias results toward underreporting of negative effects even in prospective studies many years after exposure to an abortion [15]. Another limitation of our study is that Black women, low-income women, and lower educated women (groups who are likely at greater risk of feeling pressured to have an unwanted abortion) are also somewhat unrepresented when our sample is compared to the abortion rates of these groups reported elsewhere [15]. This factor, too, suggests that our results may underestimate both the true rate of unwanted and coerced abortions and their associated negative outcomes. Therefore, any projection of the rates of negative reactions and unwanted abortions on the national population are more likely to be underestimates than overestimates. In spite of these limitations, however, the correlations between the type of abortion decision and negative effects are likely to be accurate.

Another limitation is that our data is both retrospective and limited to one point in time. Various perceptions may change, or conversely, harden over time. For example, just as victims of sexual abuse may only later recognize how they had been manipulated and abused, it is possible that some portion of the women in our sample who report that they were coerced into their abortions may have perceived their choice as freely made at that time. Similarly, there is conflicting evidence regarding the course of negative emotions over time. One case-series study based on patients recruited at three abortion clinics reported a trend towards increased negative emotions over two years [31], while ANSIRH's case series of similarly recruited patients reported a trend toward declining negative emotions [1]. But efforts to identify the differences in these finding have been blocked by both sets of authors through their refusal to provide any further details or findings beyond what they have chosen to publish or to share their data for reanalysis [5].

However, even if the trend in negative emotions could be reliably measured over the first one to five years after an abortion, case reports and other retrospective surveys have revealed that many women successfully repress negative emotions for many years, even decades [32-34]. For example, one survey of women who sought post-abortion counseling revealed that 63% reported a period of time (averaging over five years) during which they successfully denied or repressed negative feelings and doubts about their abortions [33]. Notably, for many, the successful repression of negative thoughts is often broken by some specific triggering event such as the death of a loved one, a miscarriage, or the birth of a later child [32-34]. This underscores the difficulty in attempts to measure the frequency of negative reactions facing every study design. Some women experience the bulk of their negative reactions immediately, while many (perhaps most), begin to experience negative reactions years or even decades later. Moreover, it is clear that many women who do experience negative outcomes that they attribute to their abortions often receive counseling, medication, or natural healing over time [5]. Any of these mitigating factors would dramatically reduce the degree of negative emotions that would be reported in survey responses at any specific time. This point is especially important in regard to interpreting the results of studies that employ standardized scales. For example, the ANSIRH studies employed the Brief Symptom Inventory, which asks respondents to indicate the degree, if any, of symptoms of depression or anxiety that they experienced in the seven days prior to their interview [35]. But clearly, the rate of women reporting abortion associated depression in the last seven days prior to an interview will always be far lower than the rate reported by women who were asked if they had ever experienced depression, which they attributed to their abortions. In short, while the retrospective nature of our study design introduces important limitations on the interpretation of our results, it also introduces the advantage of allowing the participants to report on their emotional and mental health experiences overall rather than just in the last seven days.

Still, we recommend that future studies should include both long-term self-assessments of symptoms women attribute to their abortion experiences alongside standardized mental health scales. The latter were not employed for this study in order to simplify the survey, reduce its length, and to reduce obstacles in the way of completing the survey. Also, while the present study was focused on how the decision rightness scales and decision type variable correlate to decision satisfaction and well-being, additional research must be done to understand better how a variety of these factors, such as moral conflict and lack of sufficient financial resources, impact mental health and decision satisfaction. Similarly, previous research has indicated that socially-based and internally-based conflicts may provide separate paths to negative emotions following an abortion [36]. The survey tools used in the present investigation may be successfully deployed to deepen our understanding of those differences.

Ideally, more prospective longitudinal studies should be undertaken which include data on prior mental health, pregnancy intention, and other confounding factors years prior to the participants' first pregnancies. Unfortunately, while a few high quality prospective studies have been done, the underlying data gathered for these studies was general in nature: The questionnaires were not designed to focus on research questions specific to the abortion experience [8,20,37]. Therefore, we recommend that new and existing national prospective survey designs should include input from experts on both sides of the abortion and mental health controversy to ensure better that the most useful questions are included. Ideally, the full range of

interactions between reproductive health experiences including abortion, natural losses, infertility, postpartum adjustments, newborn disabilities, and other interactions between these reproductive experiences, mental health, and socioeconomic well-being would be addressed in a dedicated longitudinal study, like that which was recommended by Surgeon General C. Everett Koop fully 34 years ago [33]. Better research tools will lead to greater clarity about the post-abortion experience and the needs of women exposed to unwanted abortions.

Conclusions

ANSIRH's dichotomous, yes-or-no assessment of decision rightness was too blunt of an instrument to properly assess women's satisfaction with their abortions. Both our 101-point scale for rating decision rightness and our categorical scale for identifying the type of decision (Wanted, Inconsistent, Unwanted, or Coerced) provided strong correlations to measures related to women's satisfaction with their abortion experiences. In addition, our findings suggest that ANSIRH's non-random sampling method, further compromised by a 69% refusal to participate rate, most likely lacks sufficient representation of the majority of women for whom the abortion choice is inconsistent with or violates their own values and preferences.

Our findings indicate, as a conservative estimate, that two-thirds of women experienced their abortions as a violation of their own values and preferences. A majority of women who had abortions (60%) reported they would have carried to term if they had received more support from others or had felt more financial security, and one-fourth described their abortions as either unwanted or coerced. On average, only women who described their abortions as wanted and consistent with their values and preferences (33%) attributed any benefits to their abortions. All other groups were more likely to attribute an increase in negative emotions and a decline in mental health to their abortions, report more stress when questioned about their abortion experiences, and appear less likely to participate in surveys initiated at abortion clinics as compared to women for whom the abortion is wanted and consistent with their values and preferences.

More research is needed to investigate the factors involved in abortion decisions and how these interact with both positive and negative outcomes. The finding that our simple four-point categorical scale for distinguishing between abortions that are freely wanted, accepted, unwanted, or coerced is strongly correlated with more positive or negative outcomes should be of special interest to mental health professionals and could be used as a starting point when called upon to advise pregnant patients on their abortion decisions. This scale could also be used as a guide to identifying issues that may need to be discussed when treating patients who are experiencing grief, guilt or other issues they attribute to their abortions.

Appendices

Data availability statement: The data that support the findings of this study are available from the Mendeley depository at http://dx.doi.org/10.17632/5hgj345svc.1 but are embargoed until October 1, 2023 in order to provide the authors with additional time to complete and publish additional analyses.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Sterling Institutional Review Board issued approval ID 10225. Consent was obtained or waived by all participants in this study. All procedures involving human subjects/patients were approved by Sterling Institutional Review Board issued (ID:10225). Sterling Institutional Review Board determined that this survey-based study is exempt from IRB review pursuant to the terms of the U.S. Department of Health and Human Service's Policy for Protection of Human Research Subjects at 45 C.F.R. §46.104(d). **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** David C. Reardon declare(s) employment from Elliot Institute. David C. Reardon declare(s) personal fees from Charlotte Lozier Institute. Tessa Longbons declare(s) employment from Charlotte Lozier Institute. Katherine A. Rafferty declare(s) employment from Iowa State University. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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