

Nos. 23-235 and 23-236

---

---

**In the Supreme Court of the United States**

---

U.S. FOOD AND DRUG ADMINISTRATION, ET AL.,  
PETITIONERS

*v.*

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.

---

DANCO LABORATORIES, L.L.C.,  
PETITIONER

*v.*

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.

---

**JOINT APPENDIX**  
**(Volume 2 of 2)**

---

ELIZABETH B. PRELOGAR  
*Solicitor General*  
*Department of Justice*  
*Washington, D.C. 20530-0001*  
*SupremeCtBriefs@usdoj.gov*  
*(202) 514-2217*

*Counsel of Record*  
*for the Federal Petitioners*

ERIN M. HAWLEY  
*Alliance Defending Freedom*  
*440 First Street, N.W.*  
*Suite 600*  
*Washington, D.C. 20001*  
*ehawley@adflegal.com*  
*(202) 393-8690*

*Counsel of Record*  
*for Respondents*

JESSICA L. ELLSWORTH  
*Hogan Lovells US LLP*  
*555 13th Street, N.W.*  
*Washington, D.C. 20004*  
*jessica.ellsworth@*  
*hoganlovells.com*  
*(202) 637-5600*

*Counsel of Record*  
*for Danco Laboratories, LLC*

---

---

PETITIONS FOR CERTIORARI FILED: SEPT. 12, 2023  
CERTIORARI GRANTED: DEC. 13, 2023

**TABLE OF CONTENTS**

Page

**Volume 1**

Complaint, dated Nov. 12, 2022 (ROA 74-186) ..... 1

Declaration of Mario R. Dickerson,  
dated Nov. 12, 2022 (ROA 230-235).....117

Declaration of Dr. Donna Harrison,  
dated Nov. 11, 2022 (ROA 237-249).....124

Declaration of Dr. Jeffrey Barrows,  
dated Nov. 12, 2022 (ROA 251-256).....137

Declaration of Dr. Quentin Van Meter,  
dated Nov. 11, 2022 (ROA 258-263).....144

Declaration of Dr. Christina Francis,  
dated Nov. 11, 2022 (ROA 265-273).....150

Declaration of Dr. Ingrid Skop,  
dated Nov. 11, 2022 (ROA 275-283).....159

Declaration of Dr. Nancy Wozniak,  
dated Nov. 11, 2022 (ROA 285-291).....168

Declaration of Dr. Tyler Johnson,  
dated Nov. 11, 2022 (ROA 936-941).....176

Declaration of Dr. Regina Frost-Clark,  
dated Nov. 13, 2022 (ROA 943-948).....182

Declaration of Dr. George Delgado,  
dated Nov. 14, 2022 (ROA 950-954).....188

Declaration of Dr. Shaun Jester,  
dated Nov. 14, 2022 (ROA 956-962).....194

**Volume 2**

Citizen Petition of Am. Ass'n of Pro-Life  
Obstetricians & Gynecologists to U.S. Food & Drug  
Admin., dated Aug. 20, 2002  
(ROA 354-448) (excerpts).....201



II

Table of Contents—Continued:	Page
FDA Approval Memorandum to Population Council re: NDA 20-687 Mifeprex (mifepristone), dated Sept. 28, 2000 (ROA 590-598) .....	224
FDA Approval Letter for Mifeprex (mifepristone) Tablets, dated Sept. 28, 2000 (ROA 599-602).....	233
FDA Letter to Am. Ass’n of Pro-Life Obstetricians & Gynecologists, Christian Medical & Dental Associations, and Concerned Women for America denying 2002 Citizen Petition, dated Mar. 29, 2016 (ROA 634-667).....	237
REMS for NDA 20-687 Mifeprex (mifepristone) Tablets, 200mg, dated June 8, 2011 (ROA 676-687) .....	271
FDA Letter to Danco Laboratories re: NDA 020687, Supp. 20, dated Mar. 29, 2016 (ROA 688-696) .....	283
FDA, Center for Drug Evaluation and Research, Mifepristone Summary Review, dated Mar. 29, 2016 (ROA 697-725).....	292
Citizen Petition of Am. Ass’n of Pro-Life Obstetricians & Gynecologists to FDA, dated Mar. 29, 2019 (ROA 740-766).....	321
FDA Abbreviated New Drug Application (ANDA) Approval Letter to GenBioPro, Inc., dated Apr. 11, 2019 (ROA 767-773) .....	348
FDA Supplemental Approval Letter to Danco Laboratories, LLC, dated Apr. 11, 2019 (ROA 774-781) .....	355
FDA Letter to Am. Coll. of Obstetricians & Gynecologists and Soc’y for Maternal-Fetal Med. about Mifepristone REMS, dated Apr. 12, 2021 (ROA 786-788) .....	363

### III

Table of Contents—Continued:	Page
Updated REMS Mifepristone Tablets, 200 mg, dated May 14, 2021 (ROA 796-799) .....	366
FDA Center for Drug Evaluation and Research Director Patrizia Cavazzoni Letter to Dr. Graham Chelius, dated Dec. 16, 2021 (ROA 800-801) .....	370
FDA Letter to Am. Ass’n of Pro-Life Obstetricians & Gynecologists and Am. Coll. of Pediatricians denying in part and granting in part 2019 Citizen Petition, dated Dec. 16, 2021 (ROA 802-842) .....	372
Questions and Answers on FDA’s Adverse Event Reporting System (FAERS) (ROA 843-847) .....	413
FDA, Center for Drug Evaluation and Research, Medical Review(s) of Application Number: 020687Orig1s, dated Mar. 29, 2016 (ROA 2142-2249).....	418
Mifeprex (mifepristone) Prescribing and Label Information (ROA 2361-2379) .....	526
Memorandum from FDA on Review of Supplemental Drug Applications Proposing Modifications to the Mifepristone REMS Program, dated Dec. 23, 2022 (ROA 4229) .....	545
Declaration of Dr. Donna Harrison (ROA 4230-4246).....	546

**G. WOMEN'S LIVES ARE BEING ENDANGERED BY THE LACK OF SAFEGUARDS IN FDA'S APPROVED REGIMEN**

5 On February 18, 2000, FDA informed the Population Council that “adequate information ha[d] *not* been presented to demonstrate that [mifepristone], when marketed in accordance with the terms of distribution proposed [by the Population Council], is safe and effective for use as recommended.”<sup>216</sup> Over the next several months, the Population Council and Danco refused to supplement its distribution plan with a meaningful patient safety component. This prompted  
10 FDA, on June 1, 2000, to privately convey to the sponsor a set of proposed restrictions intended to rectify the sponsor’s omission. The agency’s proposed restrictions were soon leaked to the public. Amidst a vigorous political and editorial backlash, the sponsor not only rejected FDA’s proposal but, in what was described by FDA as a “very significant change,” repudiated restrictions the sponsor itself had proposed in 1996.<sup>217</sup> FDA succumbed and soon approved a  
15 regimen that did not embody restrictions sufficient to address the agency’s legitimate safety concerns.

Early in the approval process, FDA expressed its intention to place restrictions on the use of mifepristone.<sup>218</sup> FDA’s position was informed, in part, by the international experience with

---

<sup>216</sup> 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5 (emphasis added).

<sup>217</sup> See FDA Email (June 23, 2000): at 1 (explaining that the Population Council’s attorney “affirmed that the 1996 proposals for distribution system as presented by the Pop Council then and agreed to by the [FDA Advisory Committee] and FDA are NOT what the Pop Council wants today. I explained that this change is very significant and that they need to provide their justification/rationale.”)[FDA FOIA Release: MIF 002523].

<sup>218</sup> In order to allay concerns of the drug’s European owner, FDA pledged, in the course of securing the U.S. patent rights for the Population Council, to “take appropriate measures . . . to assist through the NDA-approval process in the creation of a regime for the distribution and use that will protect against misuse of the drug.” Letter, David A. Kessler, Commissioner of Food and Drugs, to the President & CEO of Roussel Uclaf [name redacted] and to Margaret Catley-Carlson, President of Population Council (May 16, 1994): at 1 [FDA FOIA Release: MIF 004992-93].



mifepristone.<sup>219</sup> The NDA submitted by the Population Council on March 14, 1996 included a plan that would have limited distribution of mifepristone to “licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and [redacted]), who will attend educational seminars on the safe use of this regimen.”<sup>220</sup>

5 The FDA Advisory Committee, when it met in July 1996, was not satisfied with the restrictions proposed by the Population Council and expressed “serious reservations on how [the proposed drug distribution system] is currently described in terms of assuring safe and adequate credentialing of providers.”<sup>221</sup> The Committee recommended additional restrictions designed to ensure “that this drug not be expanded to hands of physicians who are not already skilled in  
10 managing pregnancies, terminations, and complications of both.”<sup>222</sup> Accordingly, FDA’s 1996 Approvable Letter required the submission of “a comprehensive description of the proposed distribution system.”<sup>223</sup>

In subsequent submissions, however, the Population Council insisted that the drug was safe and proffered restrictions designed primarily to control the manufacturing and retailing of  
15 the drug product. On August 18, 1999, the Population Council proposed to:<sup>224</sup> (i) limit the number and type of distributors; (ii) limit distribution to distributor-registered physicians who

---

<sup>219</sup> In Europe, for example, mifepristone is used under more highly controlled conditions than were ultimately required in the United States. See Amendment to NDA 20-687, International Product Labeling with English Translations (submitted March 21, 2000) (presenting English translation of mifepristone product label, approved July 6, 1999, used in Austria, Belgium, Denmark, France, Germany, Greece, the Netherlands and Spain)[FDA FOIA Release: MIF 000493-506].

<sup>220</sup> Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62].

<sup>221</sup> FDA Advisory Committee, Minutes of July 19, 1996 Meeting (approved July 23, 1996): at 7 [FDA FOIA Release: MIF 000539-45].

<sup>222</sup> FDA Memorandum, “Highlights of the July 19, 1996 Reproductive Health Products Advisory Committee (AC) Meeting on Mifepristone: Outstanding Issues for FDA to Address” (undated): at 3-4 [FDA FOIA Release: MIF 000534-38].

<sup>223</sup> 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 1.

had provided certain assurances;<sup>225</sup> and, (iii) make available “training materials and information” and medical consultation to health care providers and product information to patients.<sup>226</sup> On January 21, 2000, Danco opined that “[r]egardless of the distribution system for mifepristone, the medical safety of this drug is well documented.”<sup>227</sup> and proposed a distribution system that was  
5 designed only to ensure that Danco would “exert[ ] positive control over distribution of Mifeprex<sup>®</sup> through all phases of manufacturing, storage, shipment and administration from manufacturer to patient.”<sup>228</sup>

In reaction to the sponsor’s recalcitrance, FDA took the position “that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this  
10 product.”<sup>229</sup> The agency nevertheless continued to encourage the sponsor to take an active role in devising appropriate restrictions on the use of mifepristone. Instead, in March 2000, the Population Council again protested that such restrictions were unwarranted.<sup>230</sup> It submitted a

---

<sup>224</sup> See Medical Officer’s Review, *infra* Appendix A, at 21-23 (setting forth the Population Council’s complete response submitted to FDA on August 18, 1999).

<sup>225</sup> The physician would be required to provide a *self*-attestation covering the physician’s ability to accurately date pregnancies and determine the patient’s blood Rh factor and the physician’s access to emergency medical facilities. Registering physicians would also agree to obtain from each patient an acknowledgement that she has received full information and is willing to comply with the treatment regimen, to maintain certain records (including ultrasound and blood test records) for each patient, to report adverse events and information about ongoing pregnancies, and to “[u]se every effort to ensure patients return for their follow up visit 14-20 days after taking the product.” See Medical Officer’s Review, *infra* Appendix A, at 22-23.

<sup>226</sup> See Medical Officer’s Review, *infra* Appendix A, at 23.

<sup>227</sup> Amendment 039 to the NDA, Cover Letter, Danco to FDA (Jan. 21, 2000): at 1 [FDA FOIA Release: MIF 000525-26]. Danco attempted to attribute any deleterious effects of mifepristone abortions to misoprostol: “More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin.” *Id.* at 2.

<sup>228</sup> See Amendment 039 to the NDA, Mifeprex Distribution Plan Executive Summary (Jan. 21, 2000): at 3 [FDA FOIA Release: MIF 000530-31].

<sup>229</sup> See 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5. See *supra* Section III.C.2 and III.D. for a discussion of Subpart H, Section 314.520, which is reserved for drugs that are so inherently dangerous that their distribution and use must be restricted.

<sup>230</sup> In the course of objecting to the approval of the drug under subpart H, which is “likely to falsely ‘mark’ mifepristone as a highly toxic and risky drug,” the Population Council insisted that “the FDA knows, [Mifeprex] is



distribution plan that it characterized as “detailed and comprehensive” and “surely equal to its purpose.”<sup>231</sup> Once again, the plan consisted of restrictions intended only to control the manufacturing and retailing of the drug product.<sup>232</sup> Again FDA objected that “[t]he proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient.”<sup>233</sup> The agency requested “that sponsor present a proposal regarding provider qualifications that addresses safety concerns of patients receiving the drug product.”<sup>234</sup>

On June 1, 2000, FDA proposed the following set of “Qualifications for Physician Recipients:” (1) the physician must demonstrate that she is licensed to practice medicine; (2) the physician must be “trained and authorized by law” to perform surgical abortions; (3) the physician must have “been trained to and ha[ve] the ability to assess the age of a pregnancy accurately by ultrasound examination, to monitor abortion by ultrasound examination, and to diagnose an ectopic pregnancy by ultrasound examination;” (4) the physician must have “satisfactorily completed training certified by the distributor in the mifepristone treatment procedure, including mechanism of action, appropriate use, proper administration, follow-up, efficacy, adverse events, adverse event reporting, complications, and surgical indications;” and

---

exceptionally safe and effective.” Responses by Population Council to “FDA Letter, [redacted] to Arnold, Sandra (February 18, 2000)” (Mar. 2000): at 1 [FDA FOIA Release: MIF 000523-24] (“March 2000 Response”).

<sup>231</sup> March 2000 Response, *infra* Appendix A, at 2.

<sup>232</sup> Specifically, the plan provided for “secure manufacturing and shipping procedures, controlled returns, tracking of distribution of individual packages to the patient level, use of a limited number of distributors [redacted], account registration and other detailed ordering requirements for practitioners, direct distribution only to practitioners (not through retail pharmacies), and the use of signed patient agreements.” March 2000 Response, *infra* Appendix A, at 2.

<sup>233</sup> Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1 [FDA FOIA Release: MIF 007811-13].

<sup>234</sup> Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1. FDA wanted the sponsor to provide a set of auditable provider qualifications, a plan for auditing providers to ensure that they were meeting these criteria, and an arrangement for discontinuing distribution to unqualified providers. *See id.* at 2.

(5) the physician must have “continuing access (e.g., admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [one hour’s] drive from the treatment facility.”<sup>235</sup> FDA’s proposals were intended to address concerns about the safety of the women undergoing mifepristone-  
5 misoprostol abortions that the Population Council and Danco had refused to take into account in crafting restrictions for the drug.<sup>236</sup>

The Population Council and Danco objected strenuously to the proposed restrictions and aired their complaints in public.<sup>237</sup> FDA reprimanded the Population Council for leaking the restrictions to the public and misrepresenting the nature of the restrictions.<sup>238</sup> The Executive Vice  
10 President of the American College of Obstetricians and Gynecologists submitted an analysis of the leaked restrictions to FDA.<sup>239</sup> The editorial and political reaction,<sup>240</sup> together with the

---

<sup>235</sup> See FDA, “FDA Proposed Restricted Distribution System for NDA 20-687 on 6/1/00” (June 1, 2000)[FDA FOIA Release: MIF 000522]. See also American College of Obstetricians and Gynecologists, “Analysis of the Possible FDA Mifepristone Restrictions” (July 27, 2000): at 1 (setting forth FDA’s second proposed restriction, which is redacted in the publicly available copy of FDA’s proposal; also providing the redacted portion of the fifth restriction)[FDA FOIA Release: MIF 001366-69].

<sup>236</sup> It should be noted, that even these restrictions would not have been sufficient to make mifepristone-misoprostol abortions safe. Among the key safeguards missing from FDA’s proposal were requirements that every prospective patient undergo an ultrasound and that prescribing physicians be required to have admitting privileges at facilities able to provide emergency care.

<sup>237</sup> Paul Blumenthal, M.D., Jane Johnson, and Felicia Stewart, M.D., “The Approval of Mifepristone (RU486) in the United States: What’s Wrong with this Picture?” *Medscape Women’s Health* 5 (2000) (reproduced in an internal FDA email)[FDA FOIA Release: MIF 00002597-99] (“At a meeting of early abortion providers and abortion advocates, the Population Council and Danco revealed that the U.S. Food and Drug Administration (FDA) had made a series of proposals regarding the labeling and distribution of mifepristone that would severely limit women’s access to the drug if and when it is approved.”).

<sup>238</sup> See Teleconference Meeting Minutes (between FDA staff and representatives of the Population Council and Danco) (June 7, 2000): at 1 (“Meeting Objective: . . . to discuss the misrepresentations by the Press regarding the proposed distribution system, and to agree on the need for serious, candid, and confidential discussions to resolve deficiencies of the application.”)[FDA FOIA Release: MIF 002136-37]; FDA internal email (June 23, 2000): at 1 (re: telephone conversation with Population Council attorney, Nancy Buc, on 6/23/00) (“I also said that we were looking to Pop Council to be a responsible entity in manufacturing, distributing, and shepherding this drug and that most responsible entities make proposals rather than expect FDA to write labels and distribution systems and obtain comments through the media.”)[FDA FOIA Release: MIF 002523].

<sup>239</sup> See Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) to Jane Henney, M.D. (July 24, 2000) and enclosure: ACOG, “Analysis of the Possible FDA Mifepristone Restrictions” (July 27, 2000)[FDA FOIA Release: MIF 001366-69]. ACOG and the American Medical Association (“AMA”) also attempted to secure a meeting with



impending approval deadline of September 30, 2000,<sup>241</sup> however, had the desired effect of undermining FDA's resolve.

At a meeting on July 19, 2000, FDA yielded to the Population Council and Danco on a number of important issues.<sup>242</sup> FDA abandoned its proposal for auditable physician

5 qualifications and agreed instead to permit physicians to attest to their own qualifications.<sup>243</sup>

Instead of requiring formal training, FDA merely "request[ed] that the physician also attest to having read and understood the training materials and labeling."<sup>244</sup> FDA also agreed not to

---

Dr. Jane Henney, FDA Commissioner, and her staff, in order to further discuss their opinion of the restrictions. *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) and E. Ratcliffe Anderson, Jr., M.D. (Executive Vice President, AMA) to Jane Henney, M.D. (July 24, 2000): at 1 ("The undersigned organizations . . . are very concerned about restrictions . . . [FDA] has proposed for . . . mifepristone. . . . We would like the opportunity to meet with you and your staff to discuss this important issue. It's imperative that the FDA fully understands the effect that these proposals would have on the quality of health care. It's equally imperative that the FDA's work be based solely on evidence from the drug's clinical trials, and be entirely free from political influence.") [FDA FOIA Release: MIF 001363]. They were permitted only to meet with officials in FDA's Office of Women's Health, an office within the agency that was not involved in reviewing the NDA. *See* Letter, Jane Henney to Hale and Anderson (Aug. 11, 2000): at 1-2 [FDA FOIA Release: MIF 001361]. The questionable scientific basis for this challenge to FDA's proposed restrictions was recently brought to the attention of ACOG by one of the Petitioners. Letter, Donna Harrison, M.D. (Chairperson, AAPLOG Committee on Mifeprex Use) to Ralph Hale, M.D. (Executive Vice President, ACOG) (May 23, 2002) (available at <<http://www.aaplog.org/acogmifeprexletter.htm>>).

<sup>240</sup> *See, e.g.*, Letter, U.S. Senator Barbara Boxer to Dr. Jane Henney (June 9, 2000): at 1 ("According to news reports, the FDA is considering placing draconian restrictions on the accessibility of RU-486 as a condition of its approval . . . . In 1996, the FDA found RU-486 to be safe and effective. Therefore, it is a mystery to me why the FDA would even consider restricting access to it.") [FDA FOIA Release: MIF 006376]; Letter, Mark Green, Public Advocate for the City of New York, to Dr. Jane Henney (Sep. 22, 2000): at 1 ("Earlier this week Planned Parenthood of New York City, NARAL-New York, the Access Project and Physicians for Reproductive Health and Choice joined me in convening a public hearing in New York City on pending action by [FDA] on mifepristone . . . . [I am] also concerned about the restrictions on access to RU-486 that FDA is said to be considering.") [FDA FOIA Release: MIF 001288-1302]; Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," *New York Times* (June 8, 2000): at A21 ("The long-running effort to bring the French abortion pill to women in this country has encountered yet another obstacle: a suggestion by [FDA] that it may place tight restrictions on how the drug, RU-486, is distributed and who can prescribe it."); Letter, U.S. Representative Lynn Woolsey to Dr. Jane Henney (June 22, 2000): at 1 ("However, I am deeply concerned about recent press reports about proposed restrictions.") [FDA FOIA Release: MIF 006372].

<sup>241</sup> As noted above, because FDA had accorded priority review to mifepristone, the approval process was slated for completion by September 30, 2000.

<sup>242</sup> *See* Meeting Minutes, re: Approvability Issues Related to Labeling and Distribution Plan for Mifepristone (July 19, 2000): at 2-4 [FDA FOIA Release: MIF 004661-65].

<sup>243</sup> *See id.* at 2.

<sup>244</sup> *Id.* at 2.



require pre-procedure ultrasounds.<sup>245</sup> Furthermore, FDA stated “that it is not necessary to require the patient to take the drugs in the presence of health care provider.”<sup>246</sup>

Among the unresolved issues at the conclusion of the July 19, 2000 meeting was the question of whether prescribing physicians should be limited to those who were able to perform surgical abortions, a provider qualification FDA believed was necessary:

FDA requests that the ability to perform vacuum aspirations and/or D&Cs be added to provider qualifications. Providers also need to have access to emergency services. The need for surgical intervention is predictable unlike with other drugs. All OB/GYNs and other practitioners of women’s health have these skills. The countries with experience with mifepristone have tight provision of complete services and have a long record of good outcomes.<sup>247</sup>

The Population Council later rejected FDA’s request,<sup>248</sup> and the agency acquiesced.<sup>249</sup>

Despite its persistent concerns, FDA approved a regimen that posed the very risks to women’s health that the agency had previously identified. When it approved Mifeprex, FDA stated that “[u]nder 21 CFR 314.520, distribution of the drug is restricted as follows:”

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.

<sup>245</sup> See *id.* at 3.

<sup>246</sup> *Id.* at 3.

<sup>247</sup> *Id.* at 3.

<sup>248</sup> See Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 6 (arguing that bolstering the provider qualifications in this way would be “not only unnecessary, but also in fact potentially counterproductive for patients”)[FDA FOIA Release: MIF 0001373-81].

<sup>249</sup> See Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 [FDA FOIA Release: MIF 004587-88].

- 5
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement, and must sign it as well.
  - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
  - 10 • Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
  - Must record the Mifeprex™ package serial number in each patient's records.<sup>250</sup>

In addition, the restrictions include a requirement that distribution be carried out in accordance  
15 with the plan submitted to FDA by the Population Council in a March 30, 2000 submission.<sup>251</sup>  
Even as it assented to a regimen that lacked critical safeguards, FDA took a number of steps that  
indicated its lingering concerns about the safety of the drug. First, FDA ultimately decided to  
rely on an infrequently used provision in Subpart H in hopes of ensuring that mifepristone would  
be used safely and, if necessary, could be withdrawn from market rapidly.<sup>252</sup> Second, the staff  
20 insisted that the mifepristone label "include a black boxed warning describing the major  
requirements and conditions for use."<sup>253</sup> "FDA generally reserves boxed warnings for serious or

<sup>250</sup> Mifeprex Approval Letter at 2.

<sup>251</sup> See Mifeprex Approval Letter at 2.

<sup>252</sup> See 21 C.F.R. 530 ("Withdrawal Procedures"). See also FDA, Memorandum, re: NDA 20-687 (Feb. 17, 2000): at 3 [FDA FOIA Release: MIF 000583-85]. As late as July 19, 2000, the question of whether to use Subpart H was deemed to be an "Outstanding Issue." See Meeting Minutes, re: Approvability Issues (July 19, 2000): at 4 [FDA FOIA Release: MIF 004661-65].

<sup>253</sup> FDA, Memorandum, re NDA 20-687 (Feb. 17, 2000): at 2. The Population Council, which opposed the inclusion of such a warning, ultimately persuaded FDA to agree to a pared-down Black Box Warning, which would merely direct the prescribing physician (i) to plan in advance for emergency care, and (ii) to make available to the patient and provide her with the opportunity to discuss the patient information and patient agreement. See Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 1-2 [FDA FOIA Release MIF 0001373-81].



life-threatening risks that best can be minimized by conveying critical information to the prescribing doctor in a highlighted manner.”<sup>254</sup>

FDA’s willingness to tailor the restrictions on Mifeprex to suit the demands of the Population Council and Danco will continue to manifest itself in serious adverse events among the women who use the Mifeprex Regimen. Some of the most critical flaws in the approved regimen are discussed below along with serious adverse events that have already been reported.

**1. The Approved Regimen Is Unsafe Because It Does Not Require Ultrasound**

**a. Ultrasound Is Necessary to Accurately Date Pregnancies**

The gestational age of a woman’s pregnancy is a critical factor in determining whether she is an appropriate candidate for a mifepristone abortion. In order to minimize the risks of hemorrhage, incomplete abortion and continuing pregnancy, the gestational age of the pregnancy must be less than or equal to 49 days.<sup>255</sup> The authors of the Spitz Article, for example, found that “[f]ailures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of the pregnancy.”<sup>256</sup> Through the combination of mifepristone and

<sup>254</sup> Judith E. Beach et al., “Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs,” *Food and Drug Law Journal* 53 (1998): 403-412, at 403 (available at: <[http://www.fda.gov/pubs/Journal%20Online/53\\_3/art2.pdf](http://www.fda.gov/pubs/Journal%20Online/53_3/art2.pdf)>). See also 21 C.F.R. § 201.57(e) (“Warnings”).

<sup>255</sup> As noted above, the gestational age of a pregnancy is based on the first day of a woman’s last menstrual period, which is designated as Day 1 of the pregnancy.

<sup>256</sup> Spitz Article, *infra* Appendix A, at 1241. “The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the [less than or equal to] 49-days group to 9 percent in the 57-to-63 days group (P<0.001).” Children born from ongoing pregnancies, after a failed application of the Mifeprex Regimen, may suffer birth defects, fertility problems, or other health problems later in life. Researchers have found evidence linking misoprostol and birth defects such as missing or deformed limbs and misshapen skulls. Much of this research was conducted in Brazil, where numerous women have attempted to induce abortions using misoprostol alone. See, e.g., Sylvia Pagán Westphal, “Birth Defects Caused by Ulcer Drug Abortions,” *NewScientist.com* (29 Aug. 2001) (“Several studies in Brazil, where up to 75 percent of clandestine abortions involve misoprostol, suggest the drug causes birth defects such as fused joints, growth retardation and a condition known as Möbius syndrome, which is characterised by paralysis of the face.”); Iêda M. Orioli and Eduardo E. Castilla, “Epidemiological

misoprostol, “pregnancy was terminated in 762 of the 827 women pregnant for [less than or equal to] 49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent) . . . .”<sup>257</sup> The study also found that “[a]bdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age.”<sup>258</sup> Due to the significant increase in failures and complications with increasing gestational age, FDA approved Mifeprex only for pregnancies of less than or equal to 49 days’ gestation.<sup>259</sup>

The only way to date a pregnancy with the degree of accuracy necessary to exclude women whose pregnancies are beyond 49 days’ gestation is by use of transvaginal ultrasound.

10 FDA severely undermined the limitation on gestational age, however, when it failed to require

---

Assessment of Misoprostol Tetratogenicity,” *British Journal of Obstetrics and Gynaecology* 107 (April 2000): 519-23, at 522 (“ . . . there is an association of prenatal use of misoprostol as an abortifacient and congenital defects of vascular disruption type.”); F.R. Vargas *et al.*, “Prenatal Exposure to Misoprostol and Vascular Disruption Defects: A Case-Control Study,” *American Journal of Medical Genetics* 95 (2000): 302-306, at 306 (“add[ing] epidemiological basis to the growing body of evidence that prenatal exposure to misoprostol is related to the occurrence of vascular disruption defects in some exposed fetuses.”). FDA determined that data submitted by the Population Council from a survey of fetal abnormalities in 82 pregnancies that were exposed to mifepristone alone or in combination with misoprostol was inconclusive. See FDA Mifeprex Approval Memorandum, *infra* Appendix A, at 4. FDA acknowledged, however, the possible link between misoprostol and birth defects. See Medical Officer’s Review, *infra* Appendix A, at 18 (“ . . . medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects).”). The need for a study of the possible joint effects of mifepristone and misoprostol on babies born after a failed application of the Mifeprex Regimen was highlighted by the abnormalities discovered in a fetus exposed to misoprostol and mifepristone. See Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Number 3877547-X (March 1, 2002) (French report of numerous deformities in fetus that was exposed to mifepristone and misoprostol but survived until a subsequent surgical abortion was performed; “The anatomopathology examination showed a meningo-encephalocele. The left hand was constituted of only two fingers (oligodactylia), left and right foot were constituted of only one finger (monodactylia). There was a facial dysmorphism.”).

<sup>257</sup> Spitz Article, *infra* Appendix A, at 1241.

<sup>258</sup> Spitz Article, *infra* Appendix A, at 1241. In order to treat vaginal bleeding, “[t]wo percent of the women in the [less than or equal to] 49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids (P=0.008).” *Id.*

<sup>259</sup> FDA’s Medical Officer’s Review noted: “The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age.” Medical Officer’s Review, *infra* Appendix A, at 18. The review stated further: “This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period.” *Id.*



the ultrasound dating of pregnancies. FDA's approved regimen relies instead on a patient's recollection of her menstrual history and a physical examination. Dating based on menstrual history is inherently inaccurate because women may not have a perfect 28-day menstrual cycle<sup>260</sup> and because 25 percent of women experience bleeding during the early stages of pregnancy.<sup>261</sup>

5 Gestational dating through physical examination, even when carried out by experienced clinicians, can also be inaccurate.<sup>262</sup> Factors such as patient body size, uterine fibroids, previous parity, and uterine position may impair a clinician's ability to assess uterine size.<sup>263</sup> Transvaginal ultrasound, by contrast, is accurate within plus or minus 3 days at gestational ages of 5 to 7 weeks.<sup>264</sup> "Transvaginal ultrasonographic examination is necessary to ensure accurate gestational

---

<sup>260</sup> See, e.g., Leon Speroff, M.D., Robert H. Glass, M.D., and Nathan G. Kase, M.D., *Clinical Gynecologic Endocrinology and Infertility*, 5<sup>th</sup> ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 219 ("The perfect 28 day cycle is indeed the most common mode, but it totaled only 12.4% of Vollman's cycles. Overall, approximately 15% of reproductive age cycles are 28 days in length. Only 0.5% of women experience a cycle less than 21 days long, and only 0.9% a cycle greater than 35 days. Most women have cycles that last from 24-35 days, but at least 20% of women experience irregular cycles.").

<sup>261</sup> See Peter W. Callen, M.D., *Ultrasonography in Obstetrics and Gynecology* 2<sup>nd</sup> ed. (Phila, Pa: W.B.Saunders Company; Harcourt, Brace, Jovanovich, 1988) at 32 ("Threatened abortion is a common complication that occurs in approximately 25% of clinically apparent pregnancies."); Speroff, *et al*, *Clinical Gynecologic Endocrinology and Infertility*, 5<sup>th</sup> ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 536 (noting that "pregnancy and pregnancy-related problems such as ectopic pregnancy or spontaneous abortion" can cause uterine bleeding).

<sup>262</sup> Steven R. Goldstein, M.D., Francis R. M. Jacot, M.D., Claude Poulin, M.D., and D. Scott Poehlmann, M.D., "Documenting Pregnancy and Gestational Age," Chapter 4, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999) ("*A Clinician's Guide*"): at 41 ("Although clinical sizing of the uterus during the first trimester can provide a rough estimate of gestational age, it is imprecise; misestimation of gestational age by uterine sizing alone can occur even in the hands of experienced clinicians.").

<sup>263</sup> See *A Clinician's Guide*, *infra* Appendix A, at 41 ("a number of conditions such as leiomyomas, multiple gestation, and obesity may severely limit the accuracy of gestational age assessment by physical examination, warranting preprocedure assessment by ultrasonography in known or suspected cases") (footnotes omitted).

<sup>264</sup> See Salim Daya, M.B., "Accuracy of Gestational Age Estimation Using Fetal Crown-rump Measurements," *American Journal of Obstetrics and Gynecology* 168 (March 1993): 903-908; Ivar K. Rossavik, M.D., George O. Torjusen, M.D., and William E. Gibbons, M.D., "Conceptual Age and Ultrasound Measurements of Gestation Age and Crow-Rump Length in *in Vitro* Fertilization Pregnancies," *Fertility and Sterility* 49 (1988): 1012-17. See also Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and Gynecology* 180 (1999): 35-41. In this study comparisons of gestational age estimates based on the last reported menstrual period to those generated through ultrasound in patients presenting for medical abortion, revealed the former method to be significantly inaccurate in approximately half the cases. The authors observed: "It is interesting that in this population of women seeking abortion the gestational age according to the LMP [last menstrual period] was verified

dating for provision of medical abortion according to current standards in clinical guidelines established by the National Abortion Federation.”<sup>265</sup>

**b. Ultrasound Is Necessary to Identify Ectopic Pregnancies**

5 Approximately two percent of all pregnancies in the United States are “ectopic pregnancies,” in which the pregnancy is located outside the uterus – often in the fallopian tube.<sup>266</sup>

Mifeprex does not terminate ectopic pregnancies.<sup>267</sup> Therefore, if a woman who has an ectopic pregnancy undergoes a mifepristone-misoprostol abortion, she is at risk for tubal rupture and subsequent hemorrhage due to delay in diagnosis and delay in treatment. The symptoms of an

10 ectopic pregnancy – vaginal bleeding, pelvic pain, and cramping – are confusingly similar to certain side effects of the Mifeprex Regimen.<sup>268</sup> A woman with an ectopic pregnancy is at risk of suffering massive intra-abdominal hemorrhage, damage to her reproductive organs, permanent

---

by the transvaginal ultrasonographic examination only 48% to 56% of the time when a gestational sac was present and only 55% to 64% of the time when an embryonic pole was present . . . . These results, though, do not even include those women who were excluded from the studies because the ultrasonographic examination findings were so different from the dates by LMP that the estimation of gestational age was changed too much for them to be included.” *Id.*

<sup>265</sup> Mitchell D. Creinin, M.D. and Heather Jerald, “Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria,” *American Journal of Obstetrics and Gynecology* 180 (1999): at 35-41 (text preceding n. 8) (citation omitted).

<sup>266</sup> Centers for Disease Control, “Ectopic pregnancy – United States, 1990-1992,” *Morbidity and Mortality Weekly Report (MMWR)* 44 (No. 3) (Jan. 27, 1995): at 46. The number of ectopic pregnancies may be even higher now because sexually transmitted diseases and other causes of ectopic pregnancy are more widespread than they were in 1992 – the latest year for which the Centers for Disease Control have reported the number of ectopic pregnancies. *Id.* at 46-7.

<sup>267</sup> See, e.g., Beth Kruse *et al.*, “Management of Side Effects and Complications in Medical Abortion,” *American Journal of Obstetrics and Gynecology* 183 (2000): S65-S75, at S72 (“Mifepristone has not proved effective in treating extrauterine pregnancy . . .”).

<sup>268</sup> See American College of Obstetricians and Gynecologists, “Medical Management of Abortion,” *ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists* 26 (April 2001): at 6 (noting that in medical abortions, “women may even experience symptom resolution consistent with a complete medical abortion and still have a persistent gestational sac or even an ectopic pregnancy”) (“ACOG Practice Bulletin”). Vaginal bleeding, for example, is a normal consequence of the Mifeprex Regimen and may continue for weeks after a woman ingests Mifeprex and misoprostol. See, e.g., Spitz, *infra* Appendix A, at 1243 (“Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated



sterility, and even death if not promptly treated by emergency surgery. The authors of a French mifepristone study in which a participant with an ectopic pregnancy underwent emergency surgery to stop heavy bleeding, concluded that:

5 The case of undiagnosed ectopic pregnancy, which ruptured suddenly 2 days after misoprostol intake, indicates that (1) mifepristone plus misoprostol is not an effective treatment of ectopic pregnancies and should not be used for this purpose, and (2) all medical means of detecting an ectopic pregnancy should be used before prescribing mifepristone plus misoprostol.<sup>269</sup>

10 Although the Mifeprex Label states that the Mifeprex Regimen is contraindicated for women with a “[c]onfirmed or suspected ectopic pregnancy,”<sup>270</sup> FDA did not require that ultrasound be used to exclude women with ectopic pregnancies. Instead, the approved regimen relies solely on a self-certification by the prescribing physician that she has the “[a]bility to diagnose ectopic pregnancies.”<sup>271</sup> A physical examination alone cannot accurately identify  
15 ectopic pregnancies. Ultrasound, “[i]n addition to providing the best information for gestational age determination . . . can also provide useful diagnostic information regarding a wide variety of pathologies of early pregnancy,” including ectopic pregnancies.<sup>272</sup>

---

medically. The median duration of bleeding or spotting was 13 days in the [less than or equal to] 49-days group and 15 days in the other two groups (P<0.001).”).

<sup>269</sup> Elizabeth Aubény, *et al.*, “Termination of Early Pregnancy (Up to 63 Days of Amenorrhea) with Mifepristone and Increasing Doses of Misoprostol,” *International Journal of Fertility & Menopausal Studies* 40 (1995): 85-91, at 91.

<sup>270</sup> See Mifeprex Label (“Contraindications”).

<sup>271</sup> See Mifeprex Prescriber’s Agreement.

<sup>272</sup> *A Clinician’s Guide*, *infra* Appendix A, at 47-8.

2. **FDA's Approved Regimen Is Not Restricted to Properly Trained Physicians who Have Admitting Privileges to Emergency Facilities**

5 FDA's approved regimen lacks any objective qualifications for prescribing physicians and administering health care providers.<sup>273</sup> The health care provider administering the Mifeprex Regime need not undergo training, may not necessarily be an obstetrician or gynecologist, may not have any surgical training or training in the management of abortion complications, and may not even be a physician.<sup>274</sup> For example, the Mifeprex Regimen could be administered by a nurse  
10 untrained in any type of abortion and under the remote supervision of a family practitioner who does not regularly practice obstetrics and is incapable of providing emergency care.

Physicians and the health care staff that they supervise require formal training in both pharmaceutical and surgical abortion to minimize the morbidity inherent in performing mifepristone abortions.<sup>275</sup> National Abortion Federation guidelines provide that "[a]ll personnel  
15 performing abortions must receive training in the performance of abortions and in the prevention,

---

<sup>273</sup> Self-certifications do not provide an effective substitute for imposing objective, auditable requirements. The Mifeprex Prescriber's Agreement, for example, merely requires that the prescribing physician profess to have the "[a]bility to assess the duration of pregnancy accurately." The vacuity of this stipulation is illustrated in remarks made by Dr. Susan Allen (who later became an FDA official) before the FDA Advisory Committee. Dr. Allen stated, "If you also recall when you go through medical school you learn how to date a pregnancy." FDA Hearings Transcript, *infra* Appendix A, at 319.

<sup>274</sup> See Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 ("the distribution system would allow for physicians to obtain the drug product after meeting all qualifications, but Mifeprex could be administered by someone who is under the supervision of that physician such as midwives or nurse practitioners") [FDA FOIA Release: MIF 004587-88]; see also, Mifeprex Approval Memo, *infra* Appendix A, at 4-5 ("Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician from dispensing the drug to patients, provided state laws permit this.").

<sup>275</sup> A survey of methotrexate abortion providers underscores the necessity of training in both medical and surgical abortion. See S. Marie Harvey, Linda J. Beckman, and Sarah J. Satre, "Experiences and Satisfaction with Providing Methotrexate-Induced Abortions among U.S. Providers," *Journal of the American Medical Women's Association* 55 (2000): 161-63, at 162 (In a study comparing methotrexate and surgical abortion, "[m]ost providers felt strongly that all clinic staff should be familiar with both procedures and, thus, the training needs would be equivalent. This thought was echoed not only by physicians, who must be prepared to perform an emergency surgical abortion if methotrexate fails, but also by other clinic personnel. Thirty-nine percent of providers thought that medical abortion



recognition, and management of complications.”<sup>276</sup> Additionally, ACOG recommends that “[c]linicians other than obstetrician-gynecologists who wish to provide medical abortion services should work in conjunction with an obstetrician-gynecologist or be trained in surgical abortion in order to offer medical abortion treatment.”<sup>277</sup> The necessity for training in surgical abortion as well as mifepristone abortion stems primarily from the high failure rate of the Mifeprex Regimen. In the U.S. Clinical Trial, the Mifeprex Regimen failed for 8 percent of women with pregnancies of less than or equal to 49 days’ gestational age.<sup>278</sup>

Excessive bleeding, which is much more common following a Mifeprex abortion than a surgical abortion, is particularly likely to necessitate urgent surgical intervention. Based on an international study comparing surgical and medical abortion, FDA’s Medical Officer noted that “[o]n the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients” and characterized this as a “serious potential disadvantage of the medical method.”<sup>279</sup> In the U.S. Clinical Trial among patients whose pregnancies were of no more than 49 days’ gestation, excessive bleeding resulted in one blood transfusion, two hospitalizations, two emergency room treatments, and thirteen surgical interventions.<sup>280</sup> In

---

required more training; specifically, learning to do a vaginal ultrasound and to handle the unpredictable outcomes of methotrexate abortion required lengthy training.”)

<sup>276</sup> National Abortion Federation, “National Abortion Federation Clinical Policy Guidelines, 1998,” Appendix, in Maureen Paul et al., eds., *A Clinician’s Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999): at 256 (“*A Clinician’s Guide*”).

<sup>277</sup> ACOG Practice Bulletin, *infra* Appendix A, at 6.

<sup>278</sup> See Medical Officer’s Review, *infra* Appendix A, at Table 1. Seventeen percent of women with pregnancies of between 50 and 56 days’ gestational age and 23 percent of women with pregnancies between 56 and 63 days were failures. See *id.* In an international study reviewed by the Medical Officer, failure rates for mifepristone abortion were 5.2 percent, 8.6 percent and 16 percent in India, China and Cuba respectively, while comparable failure rates for surgical abortion were 0, 0.4 percent, and 4.0 percent. See Medical Officer’s Review, *infra* Appendix A, at 19.

<sup>279</sup> Medical Officer’s Review, *infra* Appendix A, at 19 (no citation by FDA Medical Officer).

<sup>280</sup> Medical Officer’s Review, *infra* Appendix A, at 17.

addition, 5 percent of the patients in this group received uterotonic agents to stem bleeding.<sup>281</sup> A delay in intervention may be life-threatening,<sup>282</sup> as was illustrated by the experience of one of the participants in the U.S. Clinical Trial. The treating physician described the incident to the FDA Advisory Committee:

5 In November of 1994, I was called to the [emergency room] for a woman who was bleeding due to a miscarriage, and was in obvious shock. A blood test showed that she had lost between one-half to two thirds of her blood volume . . .

I had thought she was having an incomplete miscarriage, but her husband . . . told me that she had taken RU486 approximately 2 weeks before. It was my clinical opinion that she would die soon if she did not have an immediate [dilation and curettage].

10 Without even doing the routine preparation we normally do for surgery, I realized that I had to take her immediately to surgery to save her life. I took her to the operating room and removed the contents of her uterus surgically. I gave her two units of packed red blood cells intraoperatively.

15 Even later that evening, . . . [s]he required two more units of blood because she was still orthostatic and symptomatic.<sup>283</sup>

The Mifeprex Regimen is contraindicated for “any patient who does not have adequate access to medical facilities equipped to provide emergency treatment.”<sup>284</sup> FDA’s approved regimen, however, does not require prescribing physicians to have *admitting* privileges to emergency facilities. The approved regimen requires only that a physician who is not able “to provide surgical intervention in cases of incomplete abortion or severe bleeding . . . ma[k]e 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.”<sup>285</sup> Plans for back-up care

<sup>281</sup> Medical Officer’s Review, *infra* Appendix A, at 17.

<sup>282</sup> When surgery is indicated because of acute bleeding, significant, or even life threatening blood loss, has already taken place. The preoperative preparation of the patient is often compromised in the rush to complete the surgery, which results in higher infection rates and more anesthetic complications, such as aspiration during intubation.

<sup>283</sup> FDA Hearings Transcript, *infra* Appendix A, at 223-25 (testimony of Dr. Mark Louviere).

<sup>284</sup> See Mifeprex Label (“Contraindications”).

<sup>285</sup> Mifeprex Prescriber’s Agreement. FDA, however, took two steps that suggested that it has lingering concerns about the absence of a surgical intervention qualification for Mifeprex prescribers. First, the Mifeprex Label includes a “black box” warning governing surgical back-up. Second, FDA required the Population Council to perform a post-approval study “[t]o ensure that the quality of care is not different for patients who are treated by



may be nothing more than “having the ability and responsibility to direct patients to hospitals, if needed.”<sup>286</sup> Moreover, the approved regimen does not include an objective geographical limitation to ensure that the patient has easy access to the designated emergency care facility.<sup>287</sup>

5                   **3. The Sponsor’s Recent “Dear Doctor Letter” and FDA’s Explanatory Webpage Announcing Serious Adverse Events Validate the Petitioners’ Concerns**

10                   On April 17, 2002,<sup>288</sup> Danco, with FDA’s assistance, issued a letter to health care providers to alert them to “New Safety Information,” to remind them that Mifeprex was approved for use in a prescribed regimen, and to encourage them to provide patient counseling and report adverse events.<sup>289</sup> The “New Safety Information” consisted of a number of reports of serious adverse events that had been experienced by women who were undergoing or had

---

physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention . . . .” Mifeprex Approval Memo, *infra* Appendix A, at 5.

<sup>286</sup> Mifeprex Approval Memo, *infra* Appendix A, at 5. FDA’s decision not to include a requirement that the prescribing physician have admitting privileges at a hospital could delay the patient’s admission for emergency care. Another likely consequence of not requiring the prescribing physician to have admitting privileges is underreporting of serious adverse events related to the Mifeprex Regimen. The treating physician, not privy to the Prescriber’s Agreement, may not file a serious adverse event report or notify the abortion provider of the complications that arose from the Mifeprex Regimen.

<sup>287</sup> The Chinese experience with mifepristone suggests that mifepristone should not be administered in facilities unable to provide potentially necessary emergency services. Thus, recently, the Chinese State Drug Administration responded to concerns that women were suffering as a result of lax controls on mifepristone by reiterating its policy that the drug “can only be administered at a hospital under a doctor’s supervision and cannot be sold at pharmacies even with a prescription.” See Kaiser Family Foundation, “China Reaffirms Restrictions on Unsupervised Mifepristone Use,” *Kaiser Daily Reproductive Health Report* (Oct. 15, 2001) (available at: <[http://www.kaisernet.org/daily\\_reports/rep\\_index.cfm?hint=2&DR\\_ID=7453](http://www.kaisernet.org/daily_reports/rep_index.cfm?hint=2&DR_ID=7453)>) (reporting also that, “[t]hree years ago, the Shanghai Health Bureau restricted the use of mifepristone to certain hospitals in the area because of fears of complications”).

<sup>288</sup> The letter bears the date, April 19, 2002, but was disseminated to the public on April 17, 2002.

<sup>289</sup> Danco Laboratories, Open Letter to Health Care Providers (Apr. 19, 2002) (“Dear Doctor Letter”) (available at: <[http://www.fda.gov/medwatch/SAFETY/2002/mifeprex\\_deardoc.pdf](http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf)>). Coincidentally, on the same day FDA and Danco publicized these serious adverse events, the agency also announced major changes to the Cytotec (misoprostol) label. See FDA, “Major Changes to Cytotec Labeling” (April 17, 2002). Pursuant to these labeling changes, pregnancy was removed from the list of contraindications on the Cytotec label and the black box warning cautioning pregnant women not to take the drug was also removed.

recently completed the Mifeprex Regimen.<sup>290</sup> A number of patients had suffered from ruptured ectopic pregnancies and one of these women died from hemorrhage.<sup>291</sup> The letter also reported “[t]wo cases of serious systemic bacterial infection (one fatal).”<sup>292</sup> The fatality apparently precipitated a halt in the Population Council’s Canadian clinical trials of mifepristone.<sup>293</sup> Finally, a 21 year old woman suffered a heart attack three days after she completed the Mifeprex Regimen.<sup>294</sup> These and other adverse events had been reported to FDA through its Adverse Event Reporting System (AERS).<sup>295</sup> Two of the patients who were reported to have suffered life-threatening adverse events were 15 years old.<sup>296</sup> These incidents bear out the concerns about the safety of the regimen detailed above, and the relatively high rate of serious adverse events among adolescents is of particular concern.

<sup>290</sup> The letter did not specify the number of adverse events about which Danco had been informed, but five individual cases were discussed.

<sup>291</sup> See Dear Doctor Letter, *infra* Appendix A, at 1.

<sup>292</sup> See Dear Doctor Letter, *infra* Appendix A, at 1.

<sup>293</sup> It appears that the woman reported to have died from a systemic bacterial infection was a Canadian trial subject. See Marnie Ko, “A Volunteer Dies While Testing a Controversial New Drug, Bringing the Trial to a Halt,” The Report (Oct. 8, 2001) (available at: <<http://report.ca/archive/report/20011008/p48ai011008f.html>>). See also Henry P. Kaiser Family Foundation, “Population Council Announces Death of Woman Involved in Canadian Mifepristone/Misoprostol Trial,” Daily Reproductive Health Report (Sept. 11, 2001) (available at: <[http://www.kaisernet.org/Daily\\_reports/rep\\_index.cfm?DR\\_ID=6877](http://www.kaisernet.org/Daily_reports/rep_index.cfm?DR_ID=6877)>). A *Clostridium sordellii* infection apparently caused the woman to suffer septic shock. See generally G.L. Mandell, J.E. Bennett, and R. Dolin, *Principles and Practice of Infectious Diseases* (5<sup>th</sup> ed. 2000): at 2551 (explaining that a disease process in which “clostridia clearly play a major pathogenic role i[s] uterine gas gangrene, now a rare complication that was previously seen in the setting of septic abortion.” “*C. sordellii* has been reported as a cause of uterine gas gangrene . . .”). See also FDA Q & A’s, *infra* Appendix A, at Question 3 (“Serious systemic bacterial infection is a severe life-threatening infection that spreads throughout the body and can cause death.”).

<sup>294</sup> See Dear Doctor Letter, *infra* Appendix A, at 1.

<sup>295</sup> See, e.g., Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3819498-2 (Nov. 2, 2001) (intervention to prevent permanent impairment or damage); 3806144-7 (Oct. 9, 2001) (death of a patient with an ectopic pregnancy); 3769840-6 (July 30, 2001) (hospitalization of patient with an ectopic pregnancy); 3769842-X (July 30, 2001) (intervention to prevent permanent impairment or damage); 3719885-7 (May 8, 2001) (death in conjunction with the use of misoprostol and Mifegyne, which is the trade name of mifepristone distributed in France); 3713452-7 (Apr. 27, 2001) (intervention to prevent permanent impairment or damage); and, 3769838-8 (July 30, 2001) (intervention to prevent permanent impairment or damage). The AERS depends on voluntary reporting and the accuracy of these reported adverse events cannot be verified, nor can the cause of these events be identified with certainty. There may have been other adverse events that were not reported.



Simultaneously with Danco's distribution of the *Dear Doctor Letter*, FDA published a webpage with 14 questions and answers related to mifepristone in an attempt to answer some of the questions likely to be prompted by the letter and to urge health care providers to adhere to the approved regimen.<sup>297</sup> FDA's answers, however, leave much to be desired from a medical and scientific standpoint.

First, FDA has understated the possibility that the Mifeprex Regimen caused the serious adverse events reported in the letter.<sup>298</sup> FDA did not adequately explain why women who were apparently healthy prior to undergoing the Mifeprex Regimen experienced life-threatening or fatal complications such as ruptured ectopic pregnancies, heart attacks, and systemic bacterial infections.

Second, FDA inappropriately attempted to link these adverse events to the unapproved vaginal administration of misoprostol.<sup>299</sup> It was reckless for FDA to suggest that the vaginal administration of misoprostol caused these adverse events while overlooking critical flaws in the

---

<sup>296</sup> See Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3803789-5 (Oct. 3, 2001) and 3815629-9 (Oct. 26, 2001).

<sup>297</sup> FDA, "Mifepristone Questions and Answers 4/17/2002" ("FDA Q & As") (available at: [http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa\\_4\\_17\\_02.htm](http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm)).

<sup>298</sup> See *Dear Doctor Letter*, *infra* Appendix A, at 1 ("No causal relationship between any of these events and use of Mifeprex and misoprostol has been established."). An FDA official interviewed (without attribution) downplayed the connection between the Mifeprex Regimen and the adverse events. See Susan Okie, "Physicians Sent Abortion Pill Alert: Six Women Using RU-486 Taken Ill, and Two Died, Letter Says," *Washington Post* (Apr. 18, 2002): at A2 ("These are, in fact, a very small number of events. Some of them were clearly not caused by the drug regimen.").

<sup>299</sup> The repeated references to the unapproved vaginal use of misoprostol in the FDA Q & As give rise to the inference that the reported adverse events are attributable to this single departure from the Mifeprex Regimen. See, e.g., FDA Q & As, *infra* Appendix A, at Question 1 ("In all of these cases, misoprostol was given vaginally, not orally, which is the approved regimen. FDA has not reviewed data on the safety and effectiveness of vaginal administration of misoprostol."); *id.* at Question 4 ("We do not know what role, if any, Mifeprex and 'off-label' use of vaginal misoprostol may have in developing serious infections."); *id.* at Question 9 ("Why are physicians using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses? There are published studies of the use of mifepristone with vaginal administration of misoprostol for abortion. The misoprostol doses used in these studies are higher than those described in the Mifeprex labeling . . ."); *id.* at Question 10 ("Are there risks with vaginal use of misoprostol?").

approved regimen for Mifeprex use in the United States. FDA should have first assessed essential aspects of this regimen.

It is clear, for example, that absent ultrasonographic screening for ectopic pregnancy, there is increased risk that an intact or rupturing ectopic pregnancy will be misdiagnosed as a normally progressing Mifeprex abortion. Additionally, Mifeprex abortions may be performed by practitioners who are not physicians, who cannot perform surgical abortions, or who are unable to diagnose ectopic pregnancies and their complications.

Nor is there reason to believe that systemic bacterial infection is more likely to occur following vaginal, rather than oral, administration of misoprostol. Misoprostol is commonly administered vaginally for the induction of labor without higher reported rates of either intrauterine or systemic infection when compared to orally administered misoprostol or other methods of labor induction. Rather, the occurrence of life-threatening infection in women undergoing a Mifeprex abortion should raise questions about whether prolonged genital tract bleeding in the artificial hormonal milieu created by the Mifeprex Regimen might foster or promote infectious complications. In addition, infection might occur in women who, believing that their abortion is complete and unaware that their uterus actually contains dead tissue, fail to return for follow-up visits.<sup>300</sup> This may be a particular problem when the Mifeprex Regimen is prescribed to adolescents.

The occurrence of a heart attack in a 21 year old woman is always cause for significant concern. A French woman undergoing a mifepristone abortion suffered a fatal heart attack in

---

<sup>300</sup> A. Karen Kreutner, M.D., "Postabortion Infections," *Contemporary Ob/Gyn* 1 (2001): at 37-42 ("... because medical termination may be incomplete in between 3% and 23% of patients, retained tissue and subsequent infection may go unrecognized in those lost to follow up. ... Some experts fear there will be compliance problems with the third visit, especially when the patient terminates early. In these cases, retained tissue, thought by the patient to be normal bleeding, could lead to endometritis.").



1991. A different prostaglandin (Sulprostone) administered by injection was used in that case.<sup>301</sup> This new case highlights the need for further investigation into a possible causal link between mifepristone-prostaglandin abortions and myocardial infarction.<sup>302</sup>

The ratio of serious adverse events to total uses of the Mifeprex Regimen cannot be  
5 ascertained because serious adverse event reporting is likely incomplete and because it is not publicly known how many times the Mifeprex Regimen has been used. Regardless of the relative number of serious adverse events, the nature of these events demands immediate FDA action to prevent future patient injuries and deaths.<sup>303</sup> The Joint Commission on the Accreditation of Healthcare Organizations<sup>304</sup> (“JCAHO” or “Joint Commission”) has developed  
10 an approach for investigating adverse events similar in gravity to those that prompted the issuance of the Dear Doctor Letter. The JCAHO looks for “sentinel events” which are “unexpected occurrence[s] involving death or serious physical or psychological injury, or the risk thereof.”<sup>305</sup> “Sentinel events” *signal* the need for the commencement of a “root cause

---

<sup>301</sup> See “Noticeboard: A Death Associated with Mifepristone/Sulprostone,” *Lancet* 337 (April 20, 1991): at 969-70 (“A spokeswoman for Roussel-Uclaf SA, the company that manufactures mifepristone, said ‘the death was clearly from cardiovascular shock following ‘Nalador’ (Schering) injection.’”).

<sup>302</sup> The Mifeprex Regimen should be contraindicated for women with cardiovascular risk factors until further clinical experience indicates that such contraindication is unnecessary.

<sup>303</sup> Even FDA acknowledged the rarity of the events referenced in the Dear Doctor Letter. With respect to bacterial infection, for example, FDA observed that “the rate of serious infection as a complication of pregnancy is 3.5 per 1000 pregnancies. Uterine infection occurs in 0.1-4.7% of first trimester surgical abortions and in 0.0-6.1% of medical abortions. In the past, it was most often associated with illegal abortions. It rarely occurs with pelvic surgery or even with otherwise normal childbirth.” FDA Q & A’s, *infra* Appendix A, at Question 3. FDA similarly noted the unusual nature of a heart attack in a young woman: “The single heart attack occurred in a 21 year old. A heart attack in very young women is extremely rare. . . . In 1997, the rate among US women aged 20-24 years was 0.19 per 100,000 women.” See *id.* at Question 4.

<sup>304</sup> The Joint Commission “evaluates and accredits nearly 18,000 health care organizations and programs in the United States. An independent, not-for-profit organization, JCAHO is the nation’s predominant standards-setting and accrediting body in health care. Since 1951, JCAHO has developed state-of-the-art, professionally based standards and evaluated the compliance of health care organizations against these benchmarks.” Joint Commission webpage at: <[http://www.jcaho.org/whatwedo\\_frm.html](http://www.jcaho.org/whatwedo_frm.html)>.

<sup>305</sup> Joint Commission webpage at: <[http://www.jcaho.org/sentinel/se\\_pp.html#I.SentinelEvents](http://www.jcaho.org/sentinel/se_pp.html#I.SentinelEvents)>.

analysis” of the event(s),<sup>306</sup> with the goal of developing an appropriate administrative response from the health care organization that will prevent the occurrence of future serious adverse events. A root cause analysis of sentinel events is performed before a statistically significant number of injuries or deaths occurs. It seeks to discern the facts surrounding each occurrence, distinguish factors peculiar to individuals from those pointing to procedural or administrative deficiencies, and recommend corrective measures to such systemic failures in the delivery of a particular therapy.

It is particularly important that FDA react to these sentinel events because the clinical trials underlying the approval of the Mifeprex Regimen did not adhere to FDA’s endorsed scientific methodology for such trials. The substandard trial design of the U.S. and French Clinical Trials precluded an accurate estimation of the safety of the Mifeprex Regimen compared to the existing available alternatives. Moreover, FDA did not require the sponsor to conduct rigorous Phase IV studies, which could have compensated for some of these deficiencies by generating additional safety data. The agency has not performed a root cause analysis, but has instead hastily postulated that the vaginal administration of misoprostol is the underlying cause of the adverse events.<sup>307</sup> The Petitioners believe that there are probably more scientifically sound explanations for these adverse events and that the supposed safety of the Mifeprex Regimen has been called into question. The occurrence of the adverse events related to ectopic pregnancies and life-threatening systemic bacterial infections adds significant weight to the concerns of those

---

<sup>306</sup> The Joint Commission defines “root cause analysis” as “a process for identifying the basic or causal factors that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event. A root cause analysis focuses primarily on systems and processes, not individual performance. It progresses from special causes in clinical processes to common causes in organizational processes and identifies potential improvements in processes or systems that would tend to decrease the likelihood of such events in the future, or determines, after analysis, that no such improvement opportunities exist.” Joint Commission webpage at: [http://www.jcaho.org/sentinel/se\\_pp.html#Root cause analysis](http://www.jcaho.org/sentinel/se_pp.html#Root%20cause%20analysis).



who have long warned that mifepristone-misoprostol abortions are dangerous. FDA has previously dismissed such concerns but now must respond to the accumulating evidence and act accordingly. Withdrawal of the approval is warranted.<sup>308</sup>

5           **H.     FDA’S APPROVAL OF MIFEPREX SHOULD BE WITHDRAWN  
          BECAUSE THE SPONSOR IS NOT ENFORCING THE LIMITED  
          RESTRICTIONS ON THE USE OF MIFEPREX**

          Mifeprex abortion providers openly flout the restrictions included in the approved  
10    regimen without any reaction from FDA, Danco, or the Population Council.<sup>309</sup> Shortly after  
          approval, FDA asserted that “[i]f restrictions are not adhered to, FDA may withdraw  
          approval.”<sup>310</sup> Subpart H authorizes FDA to withdraw approval of a drug approved under Section  
          314.520 if “[t]he applicant fails to adhere to the postmarketing restrictions agreed upon.”<sup>311</sup>  
          When it adopted Subpart H, FDA explained that “[t]he burden is on the applicant to ensure that

<sup>307</sup> See FDA Q & As, *infra* Appendix A, at Nos. 1, 4, 9, 10, and 11.

<sup>308</sup> The Secretary of HHS is authorized by 21 C.F.R. § 314.530(a) to withdraw approval of a Subpart H drug, subject to the applicant’s right to a hearing, if, among other things, “(3) [u]se after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug; (4) [t]he applicant fails to adhere to the postmarketing restrictions agreed upon; (5) [t]he promotional materials are false or misleading; or (6) [o]ther evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.”

<sup>309</sup> The absence of a reaction from Danco may not be surprising in light of the cavalier attitude towards the FDA approval process exhibited by Dr. Richard Hausknecht, who is Danco’s medical director. As early as July 1994, Dr. Hausknecht, had used methotrexate and misoprostol in clinical tests in the U.S. that Dr. Mitchell Creinin, a prominent abortion researcher, described as “downright unethical” and which Sandra Waldman of the Population Council described as being “very risky.” Dr. Hausknecht stopped these experiments in September 1994 when the FDA told him to “stop performing the abortions unless he gets the backing of a medical institution and submits his data and procedures to the FDA for review.” Carol Jouzaitis, “Doctor’s Abortion-Drug Technique Draws Fire,” *Chicago Tribune* (Sept. 12, 1994): at 1 & 14. Dr. Hausknecht admitted, “ ‘This is a little bit uncharted.’ . . . . But he declared: ‘Damn it. I’m not going to wait. This is a step forward. This is important. I want to see this available to women where it’s not available now.’ ” *Id.* In addition, Dr. Hausknecht’s website explains step two of the Mifeprex procedure that he employs: “At the conclusion of the [first] visit, the patient receives a packet containing tablets of misoprostol which are to be taken orally or placed in the vagina depending on the regimen you and Dr. Hausknecht choose.” Available at: <<http://www.safeabortion.com/procedure.htm>> (visited July 7, 2002). Both the home use and the vaginal administration of misoprostol contravene FDA’s approved regimen.

<sup>310</sup> See Letter, Melinda K. Plaisier, Associate Commissioner for Legislation (FDA) to Senator Tim Hutchinson (Oct. 20, 2000): at 2 [FDA FOIA Release: MIF 002648-52].

<sup>311</sup> 21 C.F.R. § 314.530(a)(4).

# Exhibit 24

2000 FDA Approval Memorandum to Population  
Council re: NDA 20-687 Mifeprex (mifepristone) (Sept.  
28, 2000)

MEMORANDUM

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

DATE: September 28, 2000

FROM:

/S/

SUBJECT:

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

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

Summary of Effectiveness and Safety

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

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

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

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



Chemistry/Manufacturing

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

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

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

Labeling

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

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

Black Box

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

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

Prescribers should make sure the patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement."

Misoprostol Administration

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

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

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

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

#### Access to Health Care and Emergency Services

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

#### Patient Agreement Form

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

#### Biopharmaceutics

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

#### Pharmacology-Toxicology

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



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

#### Medication Guide

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

#### Distribution System

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

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

#### Physician Qualifications

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

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

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

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

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

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



#### Subpart H

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

- Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately
  - Ability to diagnose ectopic pregnancies
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
  - Has read and understood the prescribing information of Mifeprex
  - Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
  - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
  - Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
  - Must record the Mifeprex package serial number in each patient's record
  
- With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:
  - Secure manufacturing, receiving, and holding areas for the drug
  - Secure shipping procedures, including tamper-proof seals
  - Controlled returns procedures
  - Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
  - Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
  - Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

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



#### Phase 4 Commitments

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

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

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

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

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

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

Public Comments Considered

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

Risk Management Program

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

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

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

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

APPEARS THIS WAY  
ON ORIGINAL



# Exhibit 25

2000 FDA Approval Letter for Mifeprex (mifepristone)  
Tablets (Sept. 28, 2000)

SEP 28 2000

NDA 20-687

Population Council  
Attention: Sandra P. Arnold  
Vice President, Corporate Affairs  
1230 York Avenue  
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, April 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative

EX. 25 pg. 01  
23-10362.600



NDA 20-687  
Page 2

purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

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

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call

[Redacted]

Sincerely,

/s/ [Redacted]

Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL



# Exhibit 27

2016 FDA Letter to Am. Ass'n of Pro-Life Obstetricians  
& Gynecologists, Christian Medical & Dental  
Associations, and Concerned Women for America  
denying 2002 Citizen Petition, Docket No. FDA-2002-P-  
0364 (Mar. 29, 2016) (2016 Petition Denial)



DEPARTMENT OF HEALTH & HUMAN SERVICES

MAR 29 2016

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

Donna Harrison, M.D.  
Executive Director  
American Association of Pro Life Obstetricians and Gynecologists  
P.O. Box 395  
Eau Claire, MI 49111

Gene Rudd, M.D.  
Senior Vice President  
Christian Medical and Dental Associations  
P.O. Box 7500  
Bristol, TN 37621

Penny Young Nance  
CEO and President  
Concerned Women for America  
1015 Fifteenth St., NW  
Suite 1100  
Washington, DC 20005

Re: Docket No. FDA-2002-P-0364

Dear Drs. Harrison and Rudd and Ms. Nance:

This letter responds to your citizen petition submitted on August 20, 2002, to the Food and Drug Administration (FDA or Agency) on behalf of the American Association of Pro Life Obstetricians and Gynecologists (AAPLOG), the Christian Medical Association (CMA) (n/k/a the Christian Medical and Dental Associations), and Concerned Women for America (CWA) (Petition).<sup>1</sup> Your Petition requests that the Agency stay FDA's approval of Mifeprex (mifepristone, also known as RU-486), thereby halting the distribution and marketing of the drug pending final action on the Petition. The Petition also requests that the Agency revoke FDA's approval of Mifeprex and requests a full audit of the French and U.S. clinical trials submitted in support of the new drug application (NDA) for Mifeprex.

We have carefully considered the information submitted in your Petition, comments on your Petition submitted to the docket, other submissions to the docket, and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your Petition is denied.

---

<sup>1</sup> The citizen petition was originally assigned docket number 2002P-0377/CP1. The number was changed to FDA-2002-P-0364 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. This citizen petition was submitted by AAPLOG, CMA, and Sandy Rios, the then-President of CWA. We have addressed this response to CWA's current CEO and President, Penny Young Nance.



## I. BACKGROUND

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets eight qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments<sup>2</sup> that the then-applicant of the Mifeprex NDA (i.e., the Population Council)<sup>3</sup> agreed to meet. In addition, the letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

## II. DISCUSSION OF ISSUES RAISED

You maintain that good cause exists for granting an immediate stay of the Mifeprex approval and for the subsequent revocation of that approval under 21 CFR 314.530 (Petition at 3). You contend that:

- The approval of Mifeprex in 2000 violated the Administrative Procedure Act's (APA's) prohibition against agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (5 U.S.C. 706(2)(A));
- The 2000 approval violated section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355) because Mifeprex does not satisfy the safety and labeling requirements of that section; and
- FDA approved Mifeprex in 2000 despite the presence of substantial risks to women's health, including fatal hemorrhage and serious bacterial infections.

You make eight arguments for the stay and revocation of the 2000 Mifeprex approval, as follows (Petition at 4-7):

---

<sup>2</sup> For purposes of this petition response, the term 'Phase 4 commitments' refers to the postmarketing studies that the Mifeprex sponsor agreed to perform as a condition of approval.

<sup>3</sup> Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco), which had been licensed to manufacture and market Mifeprex.

- That the approval of Mifeprex in 2000 violated the legal requirements of the accelerated approval regulations under 21 CFR Subpart H.
- That Mifeprex was not proven safe and effective in 2000 as required by law.
- That the Mifeprex regimen requires that Mifeprex be used in conjunction with another drug, misoprostol, which has not been separately approved as an abortifacient.
- That the Mifeprex regimen was approved in 2000 without adequate safety restrictions.
- That the drug's sponsor, following the approval in 2000, neglected to require Mifeprex providers to adhere to the restrictions contained in the regimen approved at that time.
- That the safeguards employed in one of the clinical trials that supported the 2000 approval were not mirrored in the regimen that FDA approved.
- That FDA improperly waived a requirement for pediatric studies in connection with the 2000 Mifeprex approval.
- That FDA did not require the sponsor of Mifeprex to honor its commitments for Phase 4 studies.

We respond to each of these arguments below.

We note your petition challenges the original approval of Mifeprex in 2000, and therefore this response is addressed to the 2000 approval and to the labeling that was approved at that time. Today, the Agency is approving a supplemental NDA submitted by Danco Laboratories, LLC (Danco), the holder of the Mifeprex NDA. This supplemental NDA proposed modified labeling for Mifeprex, including an updated dosing regimen, and included data to support the new labeling. After reviewing Danco's supplemental NDA, FDA determined that it met the statutory standard for approval. The fact that the previously approved regimen is no longer included in the labeling does not reflect a decision that there were safety or effectiveness concerns with the previously approved regimen.

#### **A. Approval of Mifeprex Was Consistent With Subpart H**

You maintain that FDA's 2000 approval of Mifeprex under the subpart H regulations was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, and thus violated the APA (Petition at 18-23). You state that pregnancy, without major complications, is not a serious or life-threatening illness; instead, you claim it is a normal physiological state experienced by most females one or more times and is rarely accompanied by life-threatening complications (Petition at 19). You contend that Mifeprex does not provide meaningful therapeutic benefit to patients over existing treatments because surgical abortion is a less dangerous, more effective alternative for the termination of pregnancy, and that Mifeprex does not treat any subset of the female population that is unresponsive to or intolerant of surgical abortion



(Petition at 21-23). Thus, you assert that the approval of Mifeprex did not meet the requirements for product approval under subpart H (Petition at 23).

We disagree with your conclusion that we inappropriately approved Mifeprex under subpart H. As stated in section I above, the accelerated approval regulations apply to new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (§ 314.500). As FDA made clear in the preamble to the final rule for subpart H, the subpart H regulations are intended to apply to serious or life-threatening conditions, as well as to illnesses or diseases.<sup>4</sup> The Agency also made clear that a condition need not be serious or life-threatening in all populations or in all phases to fall within the scope of these regulations.<sup>5</sup> Unwanted pregnancy falls within the scope of subpart H under § 314.500 because unwanted pregnancy, like a number of illnesses or conditions, can be serious for certain populations or under certain circumstances.

Pregnancy can be a serious medical condition in some women.<sup>6</sup> Pregnancy is the only condition associated with preeclampsia and eclampsia and causes an increased risk of thromboembolic complications, including deep vein thrombophlebitis and pulmonary embolus. Additionally, there is a significant risk of a major surgical procedure and anesthesia if a pregnancy is continued; for 2013 (the most recent data available), the Centers for Disease Control and Prevention reported an overall 32.7 percent rate of cesarean sections in the United States.<sup>7</sup> Other medical concerns associated with pregnancy include the following: disseminated intravascular coagulopathy (a rare but serious complication); amniotic fluid embolism; life-threatening hemorrhage associated with placenta previa, placenta accreta, placental abruption, labor and delivery, or surgical delivery; postpartum depression; and exacerbation or more difficult management of preexisting medical conditions (e.g., diabetes, lupus, cardiac disease, hypertension). In addition, approximately 50 percent of all pregnancies in the United States each year are unintended.<sup>8</sup> According to the

<sup>4</sup> See, e.g., 57 FR 58942, 58946 (Dec. 11, 1992).

<sup>5</sup> Id.

<sup>6</sup> According to data from the Centers for Disease Control and Prevention (CDC), for 2012 (the most recent year for which data are available), the pregnancy-related mortality ratio in the United States was 15.9 maternal pregnancy-related deaths per 100,000 live births. See CDC, Pregnancy Mortality Surveillance System, available on the CDC Web page at <http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html>. A 2012 study by Raymond and Grimes provides a comparison for the mortality rate associated with legal abortion to live birth in the United States for the earlier period from 1998 through 2005. Investigators reported that over the study period, the pregnancy related mortality rate among women who delivered live neonates was 8.8 deaths per 100,000 live births. This lower rate excludes deaths from ectopic pregnancies, stillbirths, gestational trophoblastic disease, etc. During the same period, the rate of abortion related mortality was 0.6 per 100,000 abortions. The risk of childbirth related death was therefore approximately 14 times higher than the rate associated with legal abortion. Raymond, EG and DA Grimes, Feb. 2012, The Comparative Safety of Legal Induced Abortion and Childbirth in the United States, *Obstet Gynecol*, 119 (2, Part 1):215-219.

<sup>7</sup> See CDC, Nov. 5, 2014, Trends in Low-risk Cesarean Delivery in the United States, 1990-2013, National Vital Statistics Report, 63(6), available at [http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63\\_06.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_06.pdf).

<sup>8</sup> Guttmacher Institute, Feb. 2015, Unintended Pregnancy in the United States, at 1, available at <http://www.guttmacher.org/pubs/FB-Unintended-Pregnancy-US.pdf>. See also Institute of Medicine, 2011,

Institute of Medicine, women experiencing an unintended pregnancy may experience depression, anxiety, or other conditions.<sup>9</sup>

Furthermore, consistent with § 314.500, medical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion.<sup>10</sup> Although FDA provided several examples in the preamble to the final rule to illustrate how the term “meaningful therapeutic benefit” might be interpreted, the Agency did not suggest that the meaning of the term was limited to the examples provided.<sup>11</sup> In the Phase 3 clinical trial of Mifeprex conducted in the United States, medical termination of pregnancy avoided an invasive surgical procedure and anesthesia in 92 percent of the 827 women with an estimated gestational age (EGA) of 49 days or less.<sup>12</sup> Complications of general or local anesthesia, or of intravenous sedation (“twilight” anesthesia), can include a severe allergic reaction, a sudden drop in blood pressure with cardiorespiratory arrest, death, and a longer recovery time following the procedure. Medical (non-surgical) termination of pregnancy provides an alternative to surgical abortion; it is up to the patient and her provider to decide whether a medical or surgical abortion is preferable and safer in her particular situation.<sup>13</sup>

---

Clinical Preventive Services for Women: Closing the Gaps (Closing the Gaps), at 102-110, available at [http://books.nap.edu/openbook.php?record\\_id=13181](http://books.nap.edu/openbook.php?record_id=13181) (stating that “[u]nintended pregnancy is highly prevalent in the United States”).

<sup>9</sup> See Closing the Gaps, *supra* note 8, at 103.

<sup>10</sup> For a discussion of how FDA interprets the phrase “meaningful therapeutic benefit to patients over existing treatments” in 21 CFR 314.500, see FDA guidance for industry, *Expedited Programs for Serious Conditions—Drugs and Biologics*, at 3-4, 16-17, available on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>11</sup> 57 FR 58942, 58947 (Dec. 11, 1992).

<sup>12</sup> FDA, 1999, Medical Officer’s Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion Up to 63 Day Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments (Medical Officer’s Review), at 11 (Table 1) and 16, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/20687\\_Mifepristone\\_medr\\_P1.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf) and [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/20687\\_Mifepristone\\_medr\\_P2.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P2.pdf). Spitz, IM, et al., 1998, Early Pregnancy Termination With Mifepristone and Misoprostol in the US, *NEJM*, 338:1241-1243.

<sup>13</sup> CDC data indicate that for the 730,322 abortions reported in 2011, there were 2 deaths. The CDC’s calculated case fatality rate over the period from 2008 to 2011 (the most recent year for which data are available), the case fatality rate was 0.73 legal induced abortion-related deaths per 100,000 reported legal abortions. [http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6410a1.htm?s\\_cid=ss6410a1\\_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6410a1.htm?s_cid=ss6410a1_e). Mortality rates identified by type of abortion (medical or surgical) were not available. However, the evidence suggests that the risk of mortality associated with medical abortion is quite low. Confirmation of the low risk of medical abortion is provided in a study by Trussell, et al., which recorded no deaths for 711,556 medical abortions performed by Planned Parenthood clinics under the buccal misoprostol administration protocol (Trussell J, D Nucatola, et al., Mar. 2014, Reduction in Infection-Related Mortality Since Modifications in the Regimen of Medical Abortion, *Contraception*, 89(3):193-6). We note that one study reported a comparatively high occurrence of fatality (1 death in a study of 11,155 early medical abortions); however, this apparent high occurrence of fatality is likely due to instability in the estimate as a result of the small sample size (Goldstone P, J Michelson, et al., Sept. 3, 2012, Early Medical Abortion Using Low-Dose Mifepristone Followed by



You cite a study by Jensen, et al., as support for your claim that surgical abortion is less dangerous and more effective than Mifeprex (Petition at 21-22 (citing Jensen, JT, et al., 1999, Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study, *Contraception*, 59:153-159 (Jensen study))). This study was a prospective, nonconcurrent cohort analysis comparing the patients from one site in the U.S. phase 3 trial and a separate group of patients (who were not part of the U.S. phase 3 trial) who underwent surgical abortion at the same facility. The populations that were compared were not randomized to treatment (i.e., medical or surgical abortion) and the treatment periods did not overlap.<sup>14</sup> In addition, the data on medical abortion cited in the Jensen study are based on the 178 subjects at a single site in the phase 3 U.S. Mifeprex trial that enrolled 2,121 women. This small subset of the U.S. trial included patients with pregnancies of up to 63 days' gestation. Although you cite a surgical intervention rate of 18.3 percent in the Mifeprex patients, the surgical intervention rate for Mifeprex patients with an EGA  $\leq$  49 days was 12.7 percent (9 of 71), which, because of the small number of patients in the two groups, is not statistically significantly different from the 3.9 percent rate for re-intervention in the comparative surgical group (3 of 77).<sup>15</sup> Furthermore, the 3.9 percent who first had a surgical abortion and then required surgical re-intervention ultimately required *two* surgical interventions, not one, thereby exposing them twice to the risks inherent in invasive surgical procedures and anesthesia. Finally, although you state that the medical abortion patients in the Jensen study reported significantly longer bleeding than did surgical patients, there was not a greater amount of bleeding in the medical abortion group, nor was there a significant difference between the two treatment groups in the incidence of anemia as determined by the overall change in hemoglobin concentrations.

You state that FDA "viewed [s]ubpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe" (Petition at 23 (footnote omitted)). The question of whether subpart H was "the only available regulatory vehicle" is not relevant here. As described above, Mifeprex met the criteria for approval under subpart H. Additionally, as stated in the September 28, 2000, memorandum to NDA 20-687 (Mifeprex Approval Memorandum), "the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications" that were set out in the approval letter and the Prescriber's Agreement.<sup>16</sup>

---

Buccal Misoprostol: A Large Australian Observational Study, *Med J Aust*, 197(5):282-6). Much more accurate and meaningful data are provided by Trussell's study covering >700,000 medical abortions.

<sup>14</sup> We are not suggesting that in order to be adequate and well-controlled a trial must be concurrently controlled. As discussed below in section II.B.1, FDA's regulations in § 314.126 recognize a number of different types of controls.

<sup>15</sup> In addition, the mean surgical intervention rate for all Mifeprex patients with gestational ages  $\leq$  49 days in the Phase 3 U.S. trial was 7.9 percent (65 of 827 evaluable patients).

<sup>16</sup> FDA, Sept. 28, 2000, Memorandum to NDA 20-687 MIFEPREX (mifepristone) Population Council (Mifeprex Approval Memorandum), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111366.pdf>



Furthermore, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.<sup>17</sup> The 2011 REMS for Mifeprex incorporated the restrictions under which the drug was approved. Indeed, there is substantial overlap between the requirements of subpart H and the statutory criteria for REMS set out in Title IX.

Given all of the above, the Mifeprex NDA was appropriately approved in 2000.

**B. The French and U.S. Clinical Trials of Mifeprex Provided Substantial Evidence to Support Approval**

You contend that the studies on which the Population Council relied in support of its NDA for Mifeprex do not meet the statutory and regulatory requirements for the quality and quantity of scientific evidence needed to support a finding that a new drug is safe and effective (Petition at 24).

Our review of Mifeprex was thorough and consistent with the FD&C Act and FDA regulations, including the requirements under section 505(d) of the FD&C Act that: (1) there be adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling (section 505(d)(1)) and (2) there be substantial evidence that the drug will have the effect it purports or is recommended to have under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d)(5)). The Mifeprex NDA was thoroughly reviewed, and the drug product was found to be safe and effective for its approved indication. In addition, as noted in the Mifeprex Approval Memorandum (at 1), FDA's Reproductive Health Drugs Advisory Committee (Advisory Committee) voted 6 to 0 (with 2 abstentions) on July 19, 1996, that the benefits of Mifeprex exceeded the risks. As set forth below, we disagree with your claims concerning the clinical trials that form the basis for the approval of Mifeprex.

1. The Clinical Trials Used to Support the Mifeprex NDA Were in Accordance With the FD&C Act and Applicable Regulations

You argue that because neither the French clinical trials nor the U.S. clinical trial of mifepristone were blinded, randomized, or concurrently controlled, these trials were inadequate to establish the safety and effectiveness of Mifeprex (Petition at 24-25 and 32-34). In addition, you assert in the response you submitted on October 10, 2003, to the comments in opposition to the Petition submitted by the Population Council and Danco (Response to Opposition) that the clinical trials of Mifeprex were not historically controlled but instead were uncontrolled.<sup>18</sup> You state that the

<sup>17</sup> 73 FR 16313 (Mar. 27, 2008).

<sup>18</sup> Response to Opposition at 5. You also state that because the Mifeprex regimen was the first drug regimen that FDA approved to induce abortions, the applicant should have compared the new drug regimen to surgical abortions performed during the first 49 days after a woman's last menstrual period (Response to Opposition at

applicant did not describe any historical control group in the French clinical trials, and did not indicate that any of the scientific guidelines for selecting a proper control group before beginning a historically controlled study were used for these trials (id. at 5-6). You also reject the applicant's claim that the available information on surgical abortion constitutes historically controlled data (id. at 6).

We disagree with your conclusion that the French and U.S. clinical trials of mifepristone were not clinically and legally adequate to support the approval of Mifeprex. The data from these three clinical trials (a large U.S. trial and two French trials) constitute substantial evidence that Mifeprex is safe and effective for its approved indication in accordance with section 505(d) of the FD&C Act. The labeling approved in 2000 for Mifeprex was based on data from these three clinical trials and from safety data from a postmarketing database of over 620,000 women in Europe who had had a medical termination of pregnancy (approximately 415,000 of whom had received mifepristone together with misoprostol).<sup>19</sup>

The U.S. trial of Mifeprex involved 2,121 subjects enrolled at 17 sites. Of these, 827 had an EGA of  $\leq 49$  days and were included in the efficacy evaluation.<sup>20</sup> Medical termination of pregnancy was complete (without the need for surgical intervention) in 762 of these subjects (92 percent).<sup>21</sup> Sixty-five of the subjects in the U.S. trial who were evaluable for efficacy were classified as having had a "treatment failure." The reasons for treatment failure (and number of subjects experiencing each) were: incomplete pregnancy termination (n = 39), still pregnant (n = 8), subject request for surgical intervention (n = 5), and medical indication (bleeding, n = 13).<sup>22</sup> The two French trials enrolled a total of 1,681 subjects providing effectiveness outcomes. Among the French subjects, the success rate for medical termination of pregnancy was 95.5 percent.<sup>23</sup>

In the U.S. trial, 859 subjects with an EGA of  $\leq 49$  days were evaluated for safety. Among these subjects, there were no deaths, one transfusion, and nine instances in which subjects received intravenous fluids.<sup>24</sup> The safety profile of the patient group in the French trials with an EGA of  $\leq 49$  days did not differ significantly from the safety profile of the same patient group in the U.S.

---

5, note 20). The fact that a drug might be the first one approved for a particular indication is not a factor in determining what type of control is adequate for a clinical trial of that drug for that indication. As discussed above, FDA's regulations provide for a variety of different types of controls (see 21 CFR 314.126(b)), and do not require comparison of a proposed drug product to an active control group to establish the safety and effectiveness of the drug. Therefore, the clinical trials to support the approval of Mifeprex were not required to have a surgical comparator arm.

<sup>19</sup> Mifeprex labeling, Sept. 28, 2000, PRECAUTIONS, Teratogenic Effects: Human Data, *Pregnancy*, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2000/206871bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/206871bl.pdf).

<sup>20</sup> Mifeprex Approval Memorandum, supra note 16, at 1; Medical Officer's Review, supra note 12, at 10.

<sup>21</sup> Medical Officer's Review, supra note 12, at 11 (Table 1) and 16.

<sup>22</sup> Id. at 11 (Table 1).

<sup>23</sup> Mifeprex Approval Memorandum, supra note 16, at 1.

<sup>24</sup> Medical Officer's Review, supra note 12, at 12-13.



trial, and the percentage of patients in the French and U.S. trials requiring hospitalization and blood transfusion and experiencing heavy bleeding was comparable.<sup>25</sup> There were no deaths in the French trials.<sup>26</sup>

Section 505(d) of the FD&C Act states, in part, that FDA must refuse to approve an application if the Agency finds that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the drug's proposed labeling. Section 505(d) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

As stated in 21 CFR 314.126(a), the purpose of conducting clinical investigations of a drug is to distinguish the effect of the drug from other influences, such as a spontaneous change in the course of the disease or condition, placebo effects, or biased observation. Reports of adequate and well-controlled investigations serve as the main basis for determining whether there is substantial evidence to support the claims of effectiveness for a drug.

We agree that randomization and the use of concurrent controls are two principal means of ensuring that clinical trial data are reliable and robust. However, that does not mean that in order to be adequate and well-controlled, a clinical trial must use a randomized concurrent control design. Section 314.126(b) lists the characteristics of an adequate and well-controlled study. Contrary to your assertion (Petition at 24), FDA regulations do not require that a study be blinded, randomized, and/or concurrently controlled. Among the characteristics of an adequate and well-controlled study is that it uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect (§ 314.126(b)(2)). A historical control is one of the recognized types of control (§ 314.126(b)(2)(v)), and one in which the results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment in comparable patients or populations (*id.*). Unlike some other types of control (e.g., placebo concurrent control (§ 314.126(b)(2)(i)) or dose-comparison concurrent control (§ 314.126(b)(2)(ii))), use of a historical control does not include randomization or blinding. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances, including studies in which the effect of the drug is self-evident.<sup>27</sup> Thus, in the proper setting,

---

<sup>25</sup> *Id.* at 18.

<sup>26</sup> FDA, May 21, 1996, Statistical Review and Evaluation (May 21, 1996, Statistical Review), at 4 and 7, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/20687\\_Mifepristone\\_statr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf).

<sup>27</sup> 21 CFR 314.126(b)(2)(v). We note your contention that the effects of the regimen approved in 2000 are not self-evident because "[t]he Sponsor's focus on this dyadic set of possibilities (failure (0) or success (1)) obscures a whole range of less easily measurable, but critically important, outcomes," including "tissue retention, life-threatening hemorrhaging, persistent bleeding, infection, teratogenicity, pain, continued fertility, and psychological effects" (Response to Opposition at 8). We disagree with your argument. From a clinical perspective, there are two outcomes associated with the use of Mifeprex for medical abortion: either there is a complete abortion (without the need for surgical intervention) or there is not. The "outcomes" you



historically controlled trials can be considered adequate and well-controlled, and there is no need for the other types of control listed in § 314.126(b)(2).<sup>28</sup>

The use of historical controls in the Mifeprex clinical trials was appropriate for two reasons. First, the natural history of a viable pregnancy is adequately documented (a pregnancy continues on average for 40 weeks' gestation).<sup>29</sup> Second, the effect of Mifeprex is dramatic, occurs rapidly following treatment, and has a low probability of having occurred spontaneously.<sup>30</sup> Furthermore, contrary to your assertion (Petition at 32-34), the use of a historical control in these circumstances is consistent with ICH's guidance for industry, *E10 Choice of Control Group and Related Issues in Clinical Trials* (E10 Guidance).<sup>31</sup> The E10 Guidance addresses external controls (including historical controls) that are used in externally controlled trials to compare a group of subjects receiving the test treatment with a group of patients external to the study, rather than with an internal control group consisting of patients from the same population assigned to a different treatment.<sup>32</sup> The guidance states that the "external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome)."<sup>33</sup>

---

cite are complications that can be associated with all abortions (including surgical abortion, missed abortion (non-viable pregnancy that has not been expelled from the uterus), and spontaneous abortion).

<sup>28</sup> You cite to a statement in the May 21, 1996, Statistical Review regarding the two French trials that "[i]n the absence of a concurrent control group in each of these studies, it is a matter of clinical judgement whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy" (Petition at 27). FDA's finding that Mifeprex was safe and effective for its labeled indication was based on data from three trials, one in the U.S. and two in France, as well as from safety data from a database of over 620,000 women in Europe who had had a medical termination of pregnancy (and approximately 415,000 of whom had received the combination of mifepristone and misoprostol). The Medical Officer's Review, *supra* note 12, also states that the "U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical abortions with gestations of 49 days duration or less" (Id. at 18-19). As stated previously, it is up to the physician and his/her patient to decide whether a medical or surgical abortion is preferable and safer in the patient's particular situation.

<sup>29</sup> MacDonald, PC, NF Gant, et al., 1996, *Williams Obstetrics* (20<sup>th</sup> ed.), Appleton and Lange, at 151.

<sup>30</sup> Although sources and studies differ somewhat, the 92% success rate following mifepristone/misoprostol use far exceeds the rate of spontaneous abortion (spontaneous miscarriage). One source states: "No less than 30% and as much as 60% of all conceptions abort within the first 12 weeks of gestation, and at least half of all losses go unnoticed. Most recognized pregnancy losses occur before 8 weeks' gestation, and relatively few occur after 12 weeks" (Fritz, M and L Speroff, 2011, *Clinical Gynecologic Endocrinology and Infertility* (8th ed.), Lippincott Williams & Wilkins, Philadelphia, at 1193). Other sources indicate that 15% of all pregnancies between 4-20 weeks of gestation spontaneously abort (See Speroff, L, et al., 1989, *Clinical Gynecologic Endocrinology and Infertility* (4th ed.), Williams and Wilkins, Baltimore, at 535; see also Stenchever, MA, 2001, *Comprehensive Gynecology* (4th ed.), Mosby, at 414). According to the National Library of Medicine, "[a]mong women who know they are pregnant, the miscarriage rate is about 15-20%. Most miscarriages occur during the first 7 weeks of pregnancy." (Miscarriage, available on the MedlinePlus Web site at <http://www.nlm.nih.gov/medlineplus/ency/article/001488.htm>).

<sup>31</sup> E10 Guidance, available on the FDA Drugs Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, at 6.

<sup>32</sup> Id.

<sup>33</sup> Id.

Moreover, the E10 Guidance clearly states that, notwithstanding certain limitations of external controls, including the possibility of bias, external controls can be appropriate under circumstances where the effect of the treatment is dramatic and the usual course of the disease or condition is highly predictable.<sup>34</sup> In other words, historical controls can be appropriate in circumstances such as medical termination of early pregnancy. The use of the expected rate of spontaneous abortion during early pregnancy as the control in the Mifeprex clinical trials was appropriate and fully consistent with FDA regulations and guidance. The applicant could rely on the data from the three trials to support approval because they were adequate and well-controlled, using a historical control.<sup>35</sup>

It is not uncommon for the drug product review divisions in FDA's Center for Drug Evaluation and Research (CDER) to accept for filing and approve applications that rely on clinical trials employing historical controls to support approval for drug products in which the outcome of the condition is well known and the effect of the drug is anticipated to be markedly different from that of a placebo. Examples include FDA's approval of numerous oncology drug products, including, for example, Xalkori (crizotinib) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test, and Adcetris (brentuximab vedotin) for the treatment of patients with Hodgkin lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. Other examples include iPlex (mecasermin rinfabate [rDNA origin] injection) for treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGF1D) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH; Myozyme (alglucosidase ALFA) for use in patients with Pompe disease (GAA deficiency); Ferriprox (deferiprone) for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate; Voraxaze (glucarpidase) for treatment of toxic (>1 micromole per liter) plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function; and Elelyso (taliglucerase alfa) for injection for use as a long-term enzyme replacement therapy in patients with Type 1 Gaucher disease. Similarly, it is not unusual for the CDER review divisions to accept for filing applications relying on historically controlled clinical trials. Examples of reproductive drug products for which a historical control is often relied on in the drug approval process include contraceptive drug products (e.g., most birth control pills, Mirena intrauterine device, NuvaRing (an intravaginal hormonal contraceptive), and Implanon (an implanted hormonal contraceptive)) and menopausal hormonal therapy products with the addition of a progestin to prevent endometrial cancer secondary to unopposed estrogen stimulation.

---

<sup>34</sup> Id. at 27.

<sup>35</sup> We disagree with your statement that the sponsor's failure to identify precisely a historical control group is fatal to its claim that the trials supporting the approval of Mifeprex were historically controlled (Response to Opposition at 5-6). In situations where an investigational product is anticipated to have an effect that is readily discernible and greatly exceeds that which would be expected otherwise, the historical control may be relied upon without explicitly describing it as such. Examples of situations where this arises include, as here, the use of a drug for early medical abortion, given that the majority of pregnancies continue to term, and the use of a drug as a contraceptive, given that the pregnancy rate in sexually active women between 18 and 35 years old in the absence of contraception for one year is well documented at approximately 85% (Hatcher, RA, et al., 2012, Contraception Technology (20th ed.), Ardent Media, Inc., at 780.



You state that FDA did not conduct a statistical review of the results of the U.S. clinical trial (Petition at 29). The Agency, however, concluded that the clinical results of the supporting U.S. clinical trial were “similar enough to the results of the European studies” (the studies used to support the original approval of Mifeprex in Europe) that a statistical evaluation of the results of the U.S. trial was not required.<sup>36</sup>

You maintain that the Mifeprex approval is not in accordance with Agency guidance<sup>37</sup> on when only one effectiveness trial may be necessary for approval because: (1) mifepristone had not been approved for any use in any population in the United States and (2) no one had ever presented to FDA any evidence from adequate and well-controlled trials regarding any use for mifepristone.<sup>38</sup> As stated above, our approval of Mifeprex was based on not one but three studies that met the requirements of § 314.126. Therefore, Agency guidance concerning reliance on only one effectiveness trial is not relevant to the approval of Mifeprex.

You argue that FDA’s acceptance of the French and U.S. clinical trial data violated § 314.126(e), which states that uncontrolled studies or partially controlled studies are not acceptable as the sole basis for approval of claims of effectiveness (Petition at 34-36). As explained above, the Mifeprex clinical trials were neither uncontrolled nor partially controlled. They were historically controlled, and the use of an historical control was appropriate under § 314.126(b)(2)(v). Consequently, § 314.126(e) is inapplicable.

Citing § 314.500, you contend that the approval of Mifeprex under subpart H was improper because FDA did not require the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone provides a meaningful therapeutic benefit over the standard method for terminating pregnancies (Petition at 37-40). You maintain that Mifeprex is the only drug that we have approved under § 314.520 (approval with restrictions to assure safe use) without requiring “that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials” (Petition at 37).

Nothing in subpart H requires that an applicant conduct comparative clinical trials in order to demonstrate that a drug product provides meaningful therapeutic benefit to patients over existing treatments. Furthermore, nothing in the concept of “meaningful therapeutic benefit” requires concurrent testing of a proposed drug with an existing treatment.<sup>39</sup> We have approved other drugs

---

<sup>36</sup> FDA Memorandum to NDA 20-687 re: Statistical comments on Amendment 024, Feb. 14, 2000, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/20687\\_Mifepristone\\_statr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf).

<sup>37</sup> FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Effectiveness Guidance), available on the FDA Drugs Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>38</sup> Petition at 31-32 (citing Effectiveness Guidance at 5-17).

<sup>39</sup> You state that “[c]onducting a concurrently-controlled randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable” (Petition at 32, note 145). You add that “[t]here are study designs that would have also allowed for blinding” (Id.). Assuming, arguendo, that it may have been feasible to design a randomized, concurrently-controlled study, such study was not required under our regulations; as described previously in this response, the clinical trials supporting the approval of Mifeprex

under subpart H based on clinical trials that do not directly compare the drug to an existing therapy, including Gleevec (imatinib mesylate), Tracleer (bosentan), and Xyrem (sodium oxybate). We also note that the latter two referenced drug products, Tracleer (bosentan) and Xyrem (sodium oxybate), were approved under the restricted distribution provisions at 21 CFR 314.520. As previously explained in this response, Mifeprex was deemed to have in effect an approved REMS under Title IX of FDAAA. The Mifeprex REMS, which was approved in June 2011 and is still in effect, incorporated the subpart H restrictions under which the drug was approved.

As evidenced by the foregoing, the studies supporting the 2000 approval of Mifeprex were consistent with the FD&C Act and FDA regulations, including § 314.126 and subpart H.

2. There Is No Need for an Audit of the French Clinical Data

You assert that FDA allowed “tainted data” to support the Mifeprex NDA by failing to require a comprehensive audit of the French clinical trial data after discovering violations of good clinical practices (Petition at 40-41). You maintain that we should therefore conduct a complete audit of all of the French clinical trial data to determine whether other trials must be conducted (Petition at 41 and 89).

We disagree with your characterization of both the French data and FDA’s reliance on that data. You reference the Form FDA 483 issued on June 28, 2006, to Dr. Elisabeth Aubeny, as well as the Summary of Findings related to that Form FDA 483. It is not uncommon to have trial sites receive a Form FDA 483, listing the FDA investigator’s observations regarding non-compliance with good clinical practice, at the conclusion of an inspection. The investigator will draft an Establishment Inspection Report (EIR) that reviews the violations noted and will recommend an action, taking into consideration the nature of the inspectional findings, any actions that occurred following the findings, and Agency policy. For products regulated by CDER, compliance reviewers in the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations (previously, the Division of Scientific Investigations) review the EIR, the Form FDA 483, and the evidence collected during the inspection, as well as any written response submitted timely by the inspected party, to determine whether the recommended action is appropriate and is supported by adequate evidence. This review evaluates each violation’s effect on the timeliness, accuracy, and/or completeness of the data collected from the site to ascertain if the data are reliable. In this particular case, although there were violations cited on the Form FDA 483 and discussed in the EIR, the violations were determined not to affect the reliability of the data provided by that site. The statement you quote from the Summary of Findings reflects this conclusion. We note that, although the French studies were not performed under a U.S. investigational new drug application (IND), this is typical of many approved drugs that originally were developed or studied outside the United States, and is fully permissible under 21 CFR 312.120 (Foreign clinical studies not conducted under an IND) (including the version of the provision in effect at the time of the 2000

---

were historically controlled, which was appropriate under § 314.126(b)(2)(v). Furthermore, your suggestion that there are study designs that would have allowed for blinding raises ethical issues that go beyond the scope of your Petition and this response.



approval of Mifeprex). FDA concluded that the French trials were conducted in accordance with good clinical practice,<sup>40</sup> and the Agency was able to validate the data from those studies.

It is worth noting that in 1996, when the Advisory Committee reviewed the French data without considering the U.S. data, the committee voted 6 to 2 that the French data alone demonstrated efficacy and 7 to 0 (with one abstention) that the French data supported safety.<sup>41</sup> The subsequent approval of Mifeprex was based not only on the data from the two French trials but also on the data from the large Phase 3 U.S. trial. The Advisory Committee received a report on the U.S. trial (the article by Spitz, et al., referenced in note 12 above) and had no comments.

For the foregoing reasons, there is no scientific or regulatory need for us to further review the French clinical data on Mifeprex.

### 3. Your Request for an Audit of the U.S. Clinical Data

In addition to your request that FDA conduct a full audit of the data from the French trials, you request that FDA conduct a full audit of all data from the U.S. trial (Petition at 1-2 and 89). Other than one footnote referring to a letter from the NDA sponsor to FDA (Petition at 89, note 384), you have provided no information supporting this request. Accordingly, we do not address this request further, other than to note that we do not believe there is any scientific or regulatory need to further review the U.S. clinical trial data relied on for approval of the Mifeprex NDA.

### C. FDA Lawfully Approved Labeling for Mifeprex for Use with Misoprostol

You contend that FDA's "de facto" approval of misoprostol for use with Mifeprex as part of a medical abortion regimen was unlawful because the holder of the only approved NDA for misoprostol<sup>42</sup> did not submit a supplemental NDA for this new use (Petition at 41-45). You further

---

<sup>40</sup> The regulations in effect at the time of the Mifeprex approval in 2000 refer to FDA accepting such studies when they are "well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community" FDA has generally interpreted that language as incorporating the principles of "good clinical practice" (see, e.g., ICH guidance for industry, *ICH E6 Good Clinical Practice: Consolidated Guidance* (E6 Guidance), available on the FDA Drugs Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>), which is the term used in the current regulations. The E6 Guidance states that GCP:

is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that clinical trial data are credible

(E6 Guidance at 1).

<sup>41</sup> Mifeprex Approval Memorandum, *supra* note 16, at 1.

<sup>42</sup> Two abbreviated new drug applications (ANDAs) for misoprostol have been approved since Mifeprex was approved: ANDA 076095 (IVAX Pharmaceuticals, Inc., approved July 10, 2002) and ANDA 091667 (Novel Laboratories Inc., approved July 25, 2012).

argue that FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol by overseeing the creation of Mifeprex promotional materials that discuss the off-label use of misoprostol and by disseminating information about the off-label use in documents such as the press release announcing Mifeprex's approval (Petition at 46-47).

The approval of Mifeprex was based on evidence from three adequate and well-controlled clinical trials using the treatment regimen of administration of mifepristone on day one, followed approximately 48 hours later (i.e., on day three) by the administration of misoprostol (unless a complete abortion has already been confirmed before that time). Neither the FD&C Act nor FDA regulations require the submission of a supplemental NDA by the sponsor of the misoprostol NDA for the use of misoprostol as part of the approved treatment regimen for Mifeprex. In this situation, the "drug product" subject to section 505(b) of the FD&C Act (21 U.S.C. 355(d)) was Mifeprex.<sup>43</sup> The NDA for Mifeprex appropriately contained the full reports of investigations which have been conducted to show whether or not "such drug" is effective in use (§ 505(b)(1) of the FD&C Act), and FDA appropriately found that the Mifeprex NDA met the approval requirements in § 505(d) of the FD&C Act.

There are a number of drug products that FDA has approved as safe and effective in combination with another drug for a use that was not sought by the applicant of the second drug product, and for which the Agency did not require any change in the labeling of the second product (i.e., that the second product's labeling include the indication for use with the newly approved drug product). Examples of approved drug labeling that refer to the concomitant use of another drug without there being a specific reference to the combined therapy in the previously approved labeling for the referenced drug include the following:

- Xeloda (capecitabine) for treatment of metastatic breast cancer in combination with Taxotere (docetaxel) after failure of prior anthracycline-containing therapy<sup>44</sup>

---

<sup>43</sup> In the Response to Opposition, you reference a July 2, 2002, letter submitted by the Population Council to Docket 01E-0363 re: Determination of Regulatory Review Period for Purposes of Patent Extension; Mifeprex (Response to Opposition at 12-13). In its July 2, 2002, letter, the Population Council made several statements regarding what it believed should be considered "the approved human drug product" for purposes of 21 CFR 60.22(a)(1), for purposes of patent term restoration. In the Agency's October 24, 2002, notice amending FDA's previous determination of the regulatory review period for Mifeprex (67 FR 65358), we addressed — and rejected — the Population Council's assertions. We stated that "[t]he applicant tries to characterize Mifeprex as mifepristone 'in combination with another active ingredient' in an attempt to take advantage of portions of the definition of 'human drug product' in 35 U.S.C 156(f), that is, a human drug product means 'the active ingredient of a new drug \* \* \* as a single entity or in combination with another active ingredient.' The applicant points to the definition of 'combination product' at 21 CFR 3.2(e) in this effort. A more useful description of a drug 'in combination with another active ingredient' is found at 21 CFR 300.50 (two or more drugs combined in a single dosage form). Mifeprex is not mifepristone 'in combination with another active ingredient.' Mifeprex is single entity mifepristone" (67 FR 65358, note 2).

<sup>44</sup> We note your assertion that when Xeloda and Taxotere are used together, each is being used for an FDA-approved use (Response to Opposition at 11). Taxotere (docetaxel) was approved on May 14, 1996; its current labeling states that it is indicated as a single agent for treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy, and in combination with doxorubicin and cyclophosphamide as adjuvant treatment of patients with operable node-positive breast cancer. Xeloda (capecitabine), which



Docket No. FDA-2002-P-0364

- Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin for *H. pylori* eradication
- Persantine (dipyridamole) as an adjunct to coumarin anticoagulants for prevention of postoperative thromboembolic complications of cardiac valve replacement
- Herceptin (trastuzumab) in combination with paclitaxel for treatment of metastatic breast cancer
- Vistide (cidofovir) administered with probenecid for treatment of CMV retinitis in patients with AIDS
- Daraprim (pyrimethamine) for treatment of toxoplasmosis when used conjointly with a sulfonamide

You maintain that the labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved and because it creates the false expectation that misoprostol is approved for medical abortion (Petition at 47). We disagree that the labeling for Mifeprex is misleading by virtue of the fact that it includes instructions for the use of misoprostol as part of the approved treatment regimen for Mifeprex. The Mifeprex labeling appropriately describes the clinical trial treatment regimen in which Mifeprex was shown to be safe and effective. The labeling for Mifeprex makes clear that Mifeprex tablets contain mifepristone, not misoprostol, and although the Indication and Usage section in the 2000 labeling does address the use of misoprostol in a regimen with Mifeprex, the labeling is clearly addressed to Mifeprex.

You claim that Mifeprex is misbranded because, per 21 CFR 201.6(a), the references to misoprostol in the Mifeprex labeling constitute a false or misleading representation that misoprostol itself is approved for medical termination of pregnancy (Petition at 48). In addition, you contend that Mifeprex is misbranded under section 502(j) of the FD&C Act (21 U.S.C. 352(j)) because it is unsafe when used as directed in the 2000 approved labeling (id.).

The references to misoprostol in the Mifeprex labeling do not render Mifeprex misbranded as described in § 201.6(a) because the labeling does not make any false or misleading representations with regard to misoprostol. We determined, and the labeling reflects, that Mifeprex is safe and effective for the termination of early pregnancy when used in combination with misoprostol. The approval was based on evidence from adequate and well controlled clinical trials in which misoprostol was administered two days after mifepristone to help stimulate uterine contractions; accordingly, the approved labeling describes the use of Mifeprex in combination with misoprostol.

---

originally was approved on April 30, 1998, for the treatment of metastatic breast cancer that is resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, is currently approved (in addition to other indications) for use in combination with docetaxel for treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy. The indication to which this response refers is the concomitant use (i.e., use in combination) of the two drugs, a use that is not referenced in the labeling for Taxotere. Your arguments with respect to Actos (pioglitazone) in combination with a sulfonylurea, metformin, or insulin; Viread (tenofovir disoproxil fumarate) in combination with other antiretroviral agents; and Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin (id.) are similarly inapposite.

Additionally, the approved labeling in no way implies that misoprostol alone would be safe and effective for the termination of pregnancy. Thus, the statements in the labeling are neither false nor misleading with regard to the use of misoprostol.

With regard to section 502(j) of the FD&C Act, Mifeprex is not misbranded under that provision because, as discussed in the following section, the approved regimen for Mifeprex is not “dangerous to health when used in the dosage or manner; or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.”

**D. Mifeprex Is Safe for Its Approved Use and the Conditions of Approval Do Not Lack Essential Safeguards**

You contend that FDA “approved mifepristone for use in a deregulated regimen that lacks key safeguards” (Petition at 5). You claim that in 2000, the Population Council repudiated distribution restrictions that it had proposed in 1996, and that FDA subsequently approved a regimen that does not embody restrictions sufficient to address legitimate safety concerns (Petition at 49). You note that the February 18, 2000, Mifeprex approvable letter stated that restrictions (per § 314.520) on the distribution and use of Mifeprex were needed to ensure safe use of the drug but that in March 2000, the Population Council said such restrictions were unwarranted (Petition at 51-52). You claim that we later yielded to the applicant on several important issues (Petition at 54-55).

FDA has found that Mifeprex is safe and effective for its intended use. It is true that, before the 2000 approval of Mifeprex, FDA and the applicant were not always in full agreement about the distribution restrictions. It is not unusual for such differences to emerge during the course of the review process for a proposed drug product. We ultimately determined that the distribution restrictions stated in the approval letter were appropriate to ensure the safety of Mifeprex for its intended use.<sup>45</sup> Three adequate and well-controlled clinical trials supported the safety of Mifeprex for its intended use, and over 15 years of postmarketing data and many comparative clinical trials in the United States and elsewhere continue to support the safety of this drug product.<sup>46</sup> Further, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Following is our response to the specific safety issues you raise in the Petition.

1. Ultrasound Dating

---

<sup>45</sup> We note your reference in your Response to Opposition to the statement by the Reproductive Health Drugs Advisory Committee that it had concerns about the distribution proposal discussed at the July 19, 1996, meeting (Response to Opposition at 4 (referencing the minutes from the 1996 Reproductive Health Drugs Advisory Committee meeting)). In light of FDA's determination in 2000 that the distribution restrictions stated in the approval were appropriate to ensure that Mifeprex was safe for its intended use, as well as the 2011 approval of the Mifeprex REMS, the Committee's reservations in 1996 are not applicable.

<sup>46</sup> See, e.g., Raymond, EG, et al., 2013, First-Trimester Medical Abortion With Mifepristone 200 mg and Misoprostol: A Systematic review, *Contraception*, 87:26-37 In this article, 87 trials were reviewed and 91 references were cited.



You maintain that the Mifeprex regimen is unsafe because it does not require ultrasound examination. Specifically, you maintain that the use of transvaginal ultrasound is necessary to accurately date pregnancies and to identify ectopic pregnancies, and you note both that Mifeprex was approved in 2000 only for women through 49 days' gestation and that it is contraindicated for women with a confirmed or suspected ectopic pregnancy (Petition at 57-61).

Although the protocol for the U.S. clinical trial required a transvaginal sonogram (TVS) for each patient at Visit 1 and stated that the test should be used "as indicated" at Visits 2 and 3, this does not mean that a TVS is essential to ensure the safe use of Mifeprex.<sup>47</sup> As stated in the Mifeprex Approval Memorandum, during the review process, the Agency carefully considered the role of ultrasound.<sup>48</sup> In the clinical trials, ultrasound was performed to ensure proper data collection on gestational age, but in clinical practice, pregnancies can also be (and frequently are) dated using other clinical methods. (As discussed in section II.F below, safeguards employed during clinical trials are not always essential for safe use of the approved drug product.) As part of the restricted distribution of Mifeprex put in place in 2000, each provider must have the ability to accurately assess the duration of pregnancy and to diagnose ectopic pregnancy. We determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider.

You claim that the only way to date a pregnancy accurately enough to exclude EGA > 49 days is by using TVS (Petition at 58). That is incorrect. As noted above, using TVS (or any other method) does not ensure complete accuracy in dating a pregnancy. In most cases, a provider can accurately make such a determination by performing a pelvic examination and obtaining a careful history, which would include the following: date of last menstrual period, regularity of menses, intercourse history, contraceptive history, and (if available) home pregnancy test results.<sup>49</sup> If in doubt, the provider can order an ultrasound and/or a blood test measuring the quantitative beta-human chorionic gonadotropin (hCG) to further assist in dating the gestational age.

Furthermore, use of a TVS does not guarantee that an existing ectopic pregnancy will be identified. As of April 30, 2015, there were 89 unduplicated reports in FDA's Adverse Event Reporting System (FAERS) database of ectopic pregnancy in women in the United States who had received mifepristone for termination of pregnancy since the approval of Mifeprex in the United States. In

---

<sup>47</sup> We note that the French clinical trials did not require an ultrasound examination; rather, the decision as to whether an ultrasound was needed was left to the discretion of the investigator.

<sup>48</sup> Mifeprex Approval Memorandum, *supra* note 16, at 5.

<sup>49</sup> See, e.g., Fielding, SL, et al., 2002, Clinicians' Perception of Sonogram Indication for Mifepristone Abortion up to 63 Days, *Contraception*, 66:27-31 (discussing the results of a prospective study of 1,016 women in a medical abortion trial at 15 sites that concluded that "clinicians correctly assessed gestational age as no more than 63 days in 87% of women. In only 1% (14/1013) of their assessments did clinicians underestimate gestational age. We conclude that the clinicians felt confident in not using ultrasound in most cases").

42.7% (38 of 89) of the reported cases, an ultrasound was completed. Of the 38 cases that had an ultrasound completed, 55.3% (21 of 38) showed no changes indicative of ectopic pregnancy.<sup>50</sup> In light of the fact that Mifeprex is contraindicated for women with a confirmed or suspected ectopic pregnancy, we believe it is reasonable to expect that the women's providers would not have prescribed Mifeprex if a pelvic ultrasound examination had clearly indicated an ectopic pregnancy; this strongly suggests, therefore, that ultrasound examinations were falsely negative for ectopic pregnancy in these women. The currently approved labeling for Mifeprex reflects this, stating that the "presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex."<sup>51</sup>

## 2. Physician Training and Admitting Privileges

You contend that the administration of Mifeprex should have been restricted to physicians who have formal training in both pharmaceutical and surgical abortion and who have admitting privileges to emergency facilities (Petition at 62-65).

Although we did not restrict the administration of Mifeprex to physicians with the specific requirements you list in your Petition, we did conclude in 2000 that Mifeprex had to be provided by a physician who, among other qualifications, either (1) has the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or (2) has made plans to provide such care through other qualified providers and facilities.

During the clinical trials for Mifeprex, the principal investigators were trained in surgical abortions and were able to conduct any necessary surgical interventions.<sup>52</sup> The protocol for the U.S. trial was designed such that the studies were conducted at 17 centers where the principal investigators could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.

During the NDA review process, the issue of physician qualifications and certification was thoroughly discussed within the Agency, with the applicant, and with an outside consultant with expertise in early pregnancy termination. Although the distribution of Mifeprex was not restricted to any particular medical specialist, the Agency did determine in 2000 that certain restrictions were

---

<sup>50</sup> Seventeen cases were identified as having an ultrasound with a possible ectopic pregnancy. Fourteen of these 17 (82.3%) cases noted appropriate follow-up procedures, such as additional hCG monitoring, ultrasounds, appointments, or emergency room referral, while two cases did not include any additional follow-up information. In the remaining case, a diagnosis of a heterotopic gestation (simultaneous ectopic pregnancy and intrauterine pregnancy) was noted.

<sup>51</sup> Mifeprex labeling (Mar. 29, 2016) available at [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#apphist](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist).

<sup>52</sup> Additionally, it is common in drug development that the clinical investigators who conduct pivotal Phase 3 clinical trials have more specialized training than may be necessary to ensure the safe use of a drug post-approval. Examples are trials for male erectile dysfunction (typically conducted by urologists), hypertension (internists), depression (psychiatrists), and endometriosis (gynecologists).



necessary under § 314.520. In accordance with this determination, the Prescriber's Agreement for Mifeprex stated the following:<sup>53</sup>

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have [sic] made plans to provide such care through others, and are [sic] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex....

As noted in the Mifeprex Approval Memorandum, the requirement that a physician certify, by signing the Prescriber Agreement, that he or she has the qualifications described in that Agreement limited the physicians who would be eligible to receive Mifeprex from the sponsor to those who are familiar with managing early pregnancies.<sup>54</sup> Because only such qualified physicians would be using or would oversee the use of Mifeprex, we concluded that there was no need for special certification programs or additional restrictions. Additionally, as noted in the Mifeprex Approval Memorandum, in the U.S. clinical trial of Mifeprex, 11 out of roughly 850 patients needed surgical intervention to treat bleeding, and three of these patients were treated by non-principal investigators such as emergency room physicians and a non-study gynecologist.<sup>55</sup> These data suggested that patients would receive any needed surgical intervention from either their physician or another physician with the needed skills.<sup>56</sup> The Mifeprex Approval Memorandum also pointed out that the Mifeprex labeling and the Medication Guide approved at that time highlight that surgery may be needed and that patients must understand whether the provider will furnish any necessary medical intervention or whether they will be referred to another provider and/or facility.<sup>57</sup>

In addition, one of the Phase 4 commitments accompanying the approval of Mifeprex was a cohort-based study of safety outcomes when Mifeprex is prescribed by physicians with the skills for surgical intervention compared to physicians who refer patients for surgical intervention. In a February 2008 submission, the applicant stated that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful

---

<sup>53</sup> Mifeprex labeling (June 8, 2011), Mifeprex (mifepristone) tablets, 200 mg, Prescriber's Agreement, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/020687s0141b1.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020687s0141b1.pdf).

<sup>54</sup> Mifeprex Approval Memorandum, *supra* note 16, at 5.

<sup>55</sup> *Id.*

<sup>56</sup> *Id.*

<sup>57</sup> *Id.*

study to assess this specific issue. After review of this submission, the Agency: (1) concurred with the applicant regarding the non-feasibility of conducting a meaningful study and (2) concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. Accordingly, on September 26, 2008, the Agency released the applicant from this commitment.

The provisions of the currently approved labeling (including the REMS) that relate to provider training and admitting privileges are substantially similar to the labeling provisions approved in 2000. Under current labeling, healthcare providers who administer Mifeprex must be licensed to prescribe, and must have the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also (1) be able to provide any necessary surgical intervention, or (2) have made arrangements for others to provide for such care. Healthcare providers must be able to ensure that women have access to medical facilities for emergency care, and must agree to other responsibilities, including reviewing and signing the Patient Agreement Form with the patient and providing each patient with a copy of the signed Patient Agreement Form and the Medication Guide.<sup>58</sup>

3. “Dear Health Care Provider” Letter and FDA “Mifepristone Questions and Answers”; Adverse Events Discussed in Response to Opposition

You maintain that your concerns about the safety of Mifeprex are validated by the April 19, 2002, “Dear Health Care Provider” letter issued by Danco and by statements in the “Mifepristone Questions and Answers” (Mifepristone Q&A) document (placed on FDA’s Web site on April 17, 2002) about reports of serious adverse events, including ruptured ectopic pregnancies and serious systemic bacterial infections (Petition at 65-71). You argue that FDA understated the possibility that the Mifeprex regimen caused the serious adverse events referred to in the letter and inappropriately attempted to link those events to the unapproved vaginal administration of misoprostol (Petition at 67-68).

The fact that Danco and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 (or that a subsequent Dear Health Care Provider letter and a Dear Emergency Room Director letter were issued on September 30, 2004) does not imply that the approved Mifeprex regimen is unsafe. It is not uncommon for drug sponsors to issue “Dear Health Care Provider” letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, “[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely.”<sup>59</sup> The intent of the two “Dear Health Care Provider” letters and the “Dear Emergency Room Director” letter was to provide health care personnel with new safety information regarding the use of Mifeprex. Similarly, when these letters were issued, we posted Mifepristone Q&A documents to

<sup>58</sup> Mifeprex REMS, available at

<http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=35>

<sup>59</sup> See Historical Information on Mifepristone (Marketed as Mifeprex), available at

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm>.



address questions that might arise as a result of the issuance of the letters. We disagree that we have in any way “inappropriately attempted to link” the adverse events to the intravaginal use of misoprostol. Rather, the April 2002 Mifepristone Q&A document accurately stated that in all of the adverse event cases at that time,<sup>60</sup> the misoprostol was given vaginally not orally; that we did not know what role, if any, the use of Mifeprex and vaginal misoprostol may have in the development of serious infections; and that FDA had not reviewed data on the safety and effectiveness of vaginal administration of misoprostol.

You maintain that it is particularly important for FDA to respond to these adverse events because the clinical trials in support of Mifeprex allegedly did not adhere to the Agency’s scientific methodology for such trials (Petition at 70). As explained above, however, the clinical trials supporting the approval of Mifeprex were adequate and well-controlled, and they provided substantial evidence of the safety and effectiveness of the drug product in accordance with the FD&C Act and FDA regulations.

In your Response to Opposition, you state that the serious adverse events reported to date are consistent with concerns expressed before approval (Response to Opposition at 16). You refer to the death of Holly Patterson on September 17, 2003, after she had taken Mifeprex and misoprostol to terminate her pregnancy. You state that Ms. Patterson’s apparent death from a serious systemic bacterial infection after taking Mifeprex is “not the first such death since FDA approved Mifeprex,” referring to a fatality due to serious systemic bacterial infection mentioned in the April 2002 “Dear Health Care Provider Letter” (Response to Opposition at 16-17). You also question whether adverse events for Mifeprex will be adequately reported to FDA (Response to Opposition at 18).

As with all approved drug products, we continue to monitor the safety of Mifeprex. Since the approval of Mifeprex, the Agency has issued two public health advisories (one in July 2005<sup>61</sup> and one in March 2006<sup>62</sup>) and posted multiple MedWatch safety alerts (in November 2004<sup>63</sup> and July 2005, the latter with updates in November 2005 and March 2006<sup>64</sup>). As referenced above, Danco has issued two Dear Health Care Provider letters and one Dear Emergency Room Director letter. Furthermore, since you submitted your Response to Opposition, Danco has revised the labeling for

---

<sup>60</sup> The April 2002 Mifepristone Q&A document refers to cases of ectopic pregnancy, sepsis, and heart attack.

<sup>61</sup> Available at, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051734.htm>.

<sup>62</sup> Available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051196.htm>.

<sup>63</sup> Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166463.htm>.

<sup>64</sup> Available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111339.htm>.

Docket No. FDA-2002-P-0364

Mifeprex (including the prescribing information, the Medication Guide, and the Patient Agreement), in November 2004, December 2004, July 2005, and April 2009<sup>65</sup> to provide prescribers and women with additional information about infection, vaginal bleeding, and ectopic pregnancy.

The boxed warning for Mifeprex currently states the following:

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection.** Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis.
- **Bleeding.** Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding.

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MIFEPREX REMS Program.

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol.

Advise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe MIFEPREX, so that the provider knows that she is undergoing a medical abortion.

---

<sup>65</sup> The Mifeprex labeling also was revised in June 2011 when the REMS was approved. In addition, as described above, FDA is today approving a supplemental NDA submitted by Danco that proposed modified labeling for Mifeprex. See Mifeprex labeling (Mar. 29, 2016) available at [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#aphhist](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#aphhist).



Docket No. FDA-2002-P-0364

The WARNINGS section of the Mifeprex labeling states, in part, the following:

*[With respect to infection and sepsis:]*

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established.

*Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

*[With respect to uterine bleeding:]*

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in women who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

[With respect to ectopic pregnancy:]

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

The Agency has regularly completed a cumulative summary of U.S. postmarketing adverse events reported for the use of mifepristone for medical termination of pregnancy. From the approval date of Mifeprex (September 28, 2000) through October 31, 2012, we received 2,740 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy,<sup>66</sup> including 57 reports of severe infections<sup>67</sup> and 416 incidences of blood loss requiring transfusion. From November 1, 2012, through April 30, 2015, we received 984 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy, including 9 reports of severe bacterial infections and 134 incidences of blood loss requiring transfusion.<sup>68</sup> As of April 30, 2015, 89 ectopic pregnancies associated with the use of mifepristone in the United States had been reported since the approval of Mifeprex. As of July 24, 2015, 17 U.S. deaths had been reported since the approval of Mifeprex. Deaths were associated with sepsis in 8 of the 17 reported fatalities (7 cases tested positive for *Clostridium sordellii*, and 1 case tested positive for *Clostridium perfringens*).<sup>69</sup> Seven of the eight fatal sepsis case reported vaginal misoprostol use;

<sup>66</sup> This represents data from the FDA's previous adverse event reporting system, which was known as AERS.

<sup>67</sup> Severe infections generally involve death or hospitalization for at least 2-3 days, intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, and any other physical or clinical findings, laboratory data or surgery that suggest a severe infection.

<sup>68</sup> This represents data from the current FDA Adverse Event Reporting System (FAERS), which was implemented in September 2012 and replaced AERS. FDA migrated all of the data from the previous reporting system (AERS) to FAERS. FDA validated and recoded product information as the reports from the AERS database were migrated to the FAERS database. In addition, the FAERS database features a new search functionality that is based on the date FDA initially received for the case; this facilitates more accurate follow-up for cases that have multiple reports and multiple receipt dates. For these reasons, there may be differences in the case counts between AERS and FAERS.

<sup>69</sup> We note your statements in your October 10, 2003, Response to Opposition Comments that the presence of retained products of conception can lead to the development of intrauterine or systemic infection and that Mifeprex might potentiate this possibility through negative effects on immune system function or normal protective mechanisms (Response to Opposition at 17). Regarding retained products of conception and the emergence of infections, based on autopsy and/or ultrasound reports, there were no retained products of conception in any of the eight deaths associated with infections (sepsis). With respect to your claim that Mifeprex might increase the likelihood of infection by adversely affecting immune system function, although



one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a delayed onset of toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. In the ninth case, infection was ruled out and the final autopsy report listed pulmonary emphysema as the cause of death.<sup>70</sup>

We disagree with your assertion that adverse event reporting for Mifeprex is "spotty" and that, as a result, the database for post-approval adverse events for Mifeprex is incomplete (Response to Opposition at 18). You are correct that reporting to the Agency's MedWatch program is voluntary, and we acknowledge that there is always a possibility with any drug that some adverse events are not being reported. We believe, however, that the potential for underreporting of serious adverse events associated with the use of Mifeprex for medical abortion has been very low because of the restricted distribution of the product and because healthcare providers have agreed in writing to report any hospitalizations, transfusions, or other serious adverse events associated with the drug to the sponsor, which is required under FDA's regulations to report all adverse events, including serious adverse events, to the Agency (see 21 CFR 314.80, 314.81). As with all drugs, we will continue to closely monitor the postmarketing safety data on Mifeprex.

---

published experimental data from animal models suggest that this is a theoretical possibility, the overall event rate of serious infections does not support this. If Mifeprex were adversely affecting immune system function, we would expect to see a much higher rate of serious infections from more common organisms, as well as a higher number of deaths in Europe (where mifepristone has been approved for over 24 years) and in the United States. Contrary to your statements, data from the medical literature and findings by the CDC suggest that the critical risk factor in the reported cases of sepsis is pregnancy itself (see Miech, RP, 2005, Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium sordellii*, Ann Pharmacother, 39:1483-1488). In May 2006, FDA, along with the CDC and the National Institute of Allergy and Infectious Diseases at the National Institutes of Health held a workshop on emerging clostridial disease. The issue of immunosuppression also was discussed at length during this public workshop. It was clear from the presentations at the workshop that *C. sordellii* causes rapid and serious clinical illness in settings other than medical abortion, including among pregnant women who have recently undergone spontaneous abortion or term delivery. The fact that cases of *C. sordellii* have been identified both in pregnant women who have undergone medical abortion and those who have not supports the idea that the physiology of pregnancy may be a more plausible risk factor for *C. sordellii* illness than having undergone a medical abortion with Mifeprex.

<sup>70</sup> FDA is aware of 11 additional deaths of women in foreign countries who used mifepristone for the termination of pregnancy. This included one death associated with sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial, and 10 deaths identified from post-marketing data. These 10 fatal cases were associated with the following: sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure"; thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes a jejunostomy feeding tube, and severe cystic fibrosis; *Clostridium septicum* sepsis (from a published literature report).

**E. Withdrawal of the Approval for Mifeprex Based on Current Use Is Not Appropriate**

You claim that Mifeprex abortion providers have disregarded the restrictions in the approved regimen “without any reaction from FDA, the Population Council, or Danco” (Petition at 71). You also claim that “common departures from the approved regimen” have included (1) offering the regimen to women with pregnancies beyond 7 weeks and (2) eliminating the second of the three prescribed visits to the health care provider (Petition at 72-74). You argue that we should withdraw approval of Mifeprex under § 314.530(a)(4) due to the failure of the Population Council and Danco to adhere to the postmarketing restrictions in the approval letter (Petition at 71).

In the Response to Opposition, you suggest that some providers have not met their obligations because many prescriber Web sites (1) advertise the Mifeprex regimen as being available for patients whose pregnancies have progressed beyond 49 days and (2) indicate that patients take misoprostol at home rather than at the provider’s office (Response to Opposition at 19-20). Thus, you maintain that many prescribers have allowed patients to make false statements and that the applicant is obligated to stop sales to these prescribers (*id.* at 20). You claim that prescribers have disregarded the requirements imposed with the 2000 approval of Mifeprex to provide patients with the Medication Guide, obtain their signatures on the Patient Agreement, and give them the opportunity to read and discuss these documents (*id.* at 20-21). You state that because some prescribers, with the applicant’s tacit approval, have permitted patients to sign the Patient Agreement while effectively directing them not to adhere to its requirements, the applicant cannot be described as meeting its obligations (*id.* at 21).

FDA is aware that medical practitioners may use modified regimens for administering Mifeprex and misoprostol. However, FDA does not believe that it is appropriate to initiate proceedings under 21 CFR 314.530 or section 505(e) of the FD&C Act to withdraw the approval of Mifeprex based on available information regarding the distribution of Mifeprex.

The Mifeprex approval letter included nine items that the applicant and/or prescriber were obligated to follow. As stated earlier in this response, Mifeprex has been subject to a REMS which incorporated these restrictions, including by appending a Prescriber’s Agreement outlining required qualifications and guidelines prescribers must agree to follow. Specifically, the Prescriber’s Agreement required each physician to attest to possessing certain necessary skills and abilities related to managing early pregnancy to ensure safe use of the drug.<sup>71</sup> The Prescriber’s Agreement also contained responsibilities that prescribers must carry out.<sup>72</sup> The Prescriber’s Agreement stated that prescribers must have read and understood the prescribing materials.<sup>73</sup>

---

<sup>71</sup> Prescriber’s Agreement, *supra* note 53, at 1.

<sup>72</sup> *Id.* at 1-2.

<sup>73</sup> *Id.* at 1.



The 2000 Prescriber's Agreement also required that the prescriber (1) provide each patient with a copy of the Medication Guide and the Patient Agreement, (2) fully explain the procedure to the patient, and (3) give the patient the opportunity to read and discuss the Medication Guide and Patient Agreement.<sup>74</sup> The Medication Guide and the Patient Agreement stated the approved dosage and administration of Mifeprex. FDA has no evidence, nor have you provided any evidence, that prescribers have not signed the Prescriber's Agreement, or that women either have not been given the opportunity to read and discuss the Patient Agreement or have not signed the Patient Agreement.

As noted above, restrictions on the distribution and use of Mifeprex substantially similar to those approved in 2000 remain in place today.

**F. Safeguards Employed in Clinical Trials Are Not Necessarily Essential Conditions for Approval**

You maintain that we effectively approved a drug regimen that we had not tested because the Mifeprex regimen approved in 2000 does not include important safeguards employed in the U.S. clinical trial (e.g., governing physician training, use of ultrasound, 4-hour post-misoprostol monitoring, physician privileges at facilities that provide emergency care) (Petition at 75-76). You argue that we should not have extrapolated conclusions about the safety and effectiveness of the Mifeprex regimen from data generated under trial conditions that do not mirror the approved regimen (id.).

We disagree with your assertions. Furthermore, your implication that the approved conditions of use for a drug product must mirror those used in the clinical trials supporting its approval is incorrect. As discussed above with respect to ultrasound dating and physician qualifications, safeguards employed in clinical trials are often not reflected in approved drug product labeling nor are they necessarily needed for the safe and effective use of the drug product after approval. Many clinical trial designs are more restrictive (e.g., additional laboratory and clinical monitoring, stricter inclusion and exclusion criteria, more visits) than will be necessary or recommended in postapproval clinical use; this additional level of caution is exercised until the safety and efficacy of the product is demonstrated. For example, in menopause hormonal therapy trials, specialists perform periodic endometrial biopsies to establish the safety of long-term hormone use. Once the safety of the product has been established, these biopsies are not recommended in the approved product labeling, nor are they routinely performed in actual use with the approved product. During our review of the clinical data submitted in support of an NDA, we make an assessment of the procedures employed during the clinical trials and the conditions under which the drug was studied. This assessment is reflected in the approved labeling for the drug product.

Upon reviewing the data submitted in support of the Mifeprex NDA, we concluded in 2000 that restrictions requiring ultrasound dating of gestational age of the pregnancy and limiting access to Mifeprex to physicians trained in surgical abortions and capable of performing surgical intervention if complications arise subsequent to use of Mifeprex were not necessary to ensure its safe use (see discussion in section II.D above).

---

<sup>74</sup> Id.

**G. FDA Appropriately Concluded That Studies of Mifeprex in Pediatric Patients Were Unnecessary**

You maintain that our 2000 approval of Mifeprex violated regulations requiring that new drugs be tested for safety and effectiveness in the pediatric population (Petition at 76). You state that although we stated in the September 28, 2000, approval letter that the application was subject to the Pediatric Rule (21 CFR 314.55), we waived the requirement without explanation (Petition at 78). You contend that the Mifeprex application was not in accordance with any of the three provisions under which an applicant may obtain a waiver under 21 CFR 314.55(c)(2) of the pediatric study requirement, for the following reasons:

- 21 CFR 314.55(c)(2)(i) does not apply because FDA maintained that Mifeprex represented a meaningful therapeutic benefit over existing treatments and because Mifeprex can be expected to be used in a substantial number of pediatric patients.
- 21 CFR 314.55(c)(2)(ii) does not apply because pediatric studies of Mifeprex would not have been either impossible or highly impractical because a large population of pediatric females becomes pregnant each year and the female population is evenly distributed throughout the country.
- 21 CFR 314.55(c)(2)(iii) does not apply because FDA stated that there was no reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen than older females (Petition at 79-82).

As an initial matter, we reject your contention that the Population Council did not provide evidence from any adequate and well-controlled adult studies of Mifeprex, and that therefore it was inappropriate to rely on the submitted adult studies under § 314.55(a) with respect to the use of Mifeprex in the pediatric population (Petition at 82). As discussed above, the Mifeprex approval was based on three adequate and well-controlled clinical trials.

Our conclusion that studies of Mifeprex in pediatric patients were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time.<sup>75</sup> We determined that there were sufficient data from studies of mifepristone. Therefore, the Mifeprex approval letter should have stated our conclusion that the pediatric study requirements were waived for pre-menarchal patients and that the pediatric study requirements were met for post-menarchal pediatric patients, rather than stating that we were waiving the requirements for all pediatric age groups.<sup>76</sup>

---

<sup>75</sup> FDA was enjoined from enforcing 21 CFR § 314.55 under *Ass'n of Am. Physicians & Surgeons v. FDA*, 226 F. Supp. 204 (D.D.C. 2002). However, on December 3, 2003, the President signed into law the Pediatric Research Equity Act of 2003 (PREA 2003), Public Law 108-155, which gave FDA the statutory authority to require pediatric studies of drugs when such studies are needed to ensure the safe and effective use of drugs in children. PREA 2003 stated that any waivers or deferrals that were granted under the Pediatric Rule were considered to be granted under PREA 2003 (see Section 4 of Public Law 108-155).

<sup>76</sup> FDA's implementation of the Pediatric Rule was still at a relatively early stage in September 2000 and the Agency was not always precise regarding the language used in approval letters to distinguish between situations where studies were waived and where studies were not needed because the requirements were met.



Docket No. FDA-2002-P-0364

It is still our scientific opinion, based on the medical literature and over 15 years of use in the United States, that there is no biological reason to expect menstruating females under age 18 — compared to women age 18 and older — to have a different physiological outcome with the Mifeprex regimen.<sup>77</sup>

#### **H. The Mifeprex Approval Letter Included Appropriate Phase 4 Commitments**

You state that although the Population Council agreed in 1996 to perform Phase 4 studies with six different objectives, the Mifeprex approval letter included only two Phase 4 study obligations (Petition at 85-86). You allege that the changes in its Phase 4 commitments were largely in response to the Population Council's unwillingness to explore the "ramifications" of the Mifeprex regimen (Petition at 87). You maintain that this alleged "curtailment" of Phase 4 study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (Petition at 88).<sup>78</sup>

We disagree with your assertions. Our process for determining the appropriate Phase 4 studies for Mifeprex adequately addressed our concerns and reflected typical Agency-applicant interactions to reach consensus on appropriate postmarketing studies.<sup>79</sup> It is common for proposed Phase 4 commitments to evolve during the application review process. As you note (Petition at 85), in 1996, the Population Council committed to six postmarketing studies with the following objectives:

---

<sup>77</sup> In the Mifeprex Approval Memorandum, the Office Director stated, "FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients" (Mifeprex Approval Memorandum, *supra* note 16, at 7).

<sup>78</sup> We note that post-marketing studies are not required for approvals under 21 CFR 314.520.

<sup>79</sup> You also state that, "[a]s a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects" (Petition at 84). This argument is not relevant to Mifeprex, which is approved for medical termination of pregnancy. Mifeprex is not approved for long-term or chronic use, which is an important factor in assessing the need to study long-term effects of a drug. Long-term safety for a single-dose medication is generally not a concern. However, FDA routinely monitors postmarketing safety data for all approved drugs. Mifeprex is no exception. FDA's Office of Surveillance and Epidemiology continuously monitors available safety data from use of mifepristone for termination of pregnancy both within and outside of the United States and has not identified any long-term safety signals. The Mifeprex adverse events reported are consistent with product labeling and with what can be expected with spontaneous and surgical abortions. Furthermore, as explained in this response, since Mifeprex's approval, safety concerns and adverse events have been monitored through enhanced surveillance and reporting by certified prescribers, and we have required a REMS for Mifeprex including a Medication Guide, elements to assure safe use, an implementation system that requires the sponsor to assess the performance of certified distributors, and a timetable for submission of assessments of the REMS. We also continue to closely monitor the post-marketing safety of mifepristone for termination of pregnancy for any new or long-term signals.

Docket No. FDA-2002-P-0364

- (1) Monitor the adequacy of the distribution and credentialing system.
- (2) Follow-up on the outcome of a representative sample of Mifeprex-treated women who have surgical abortion because of method failure.
- (3) Assess the long-term effects of multiple use of the regimen.
- (4) Ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
- (5) Study the safety and efficacy of the regimen in women under age 18, women over age 35, and women who smoke.
- (6) Ascertain the effect of the regimen on children born after treatment failure.

As stated in the Mifeprex Approval Memorandum (at 7), during the final review of the Mifeprex NDA in 2000, items 1, 2, 4, and 5 above were revised and integrated into a single Phase 4 study to assess whether, for providers who did not have surgical intervention skills and referred patients for surgery, clinical outcomes were similar to those of patients under the care of physicians (such as those in the clinical trials) who possessed surgical skills. Based on a revised protocol, this Phase 4 study would monitor the adequacy of provider qualifications (item 1) and collect data on safety outcomes and method failures (item 2) and return of patients for their follow-up visits (item 4). Because patients would not be restricted to a specific age range or smoking status, information to address item 5 also would be obtained. In a second Phase 4 study, the applicant would examine the outcomes of ongoing pregnancies (i.e., method failures) through a surveillance, reporting, and tracking system (item 6). Thus, although the approval letter listed only two Phase 4 studies, those two studies incorporated all but one element of the six studies listed in the September 18, 1996, approvable letter concerning the Mifeprex NDA. (As discussed below, the remaining study was not included for logistical and practical reasons.)

As mentioned in section II.D.2 above, for the first Phase 4 study, which addressed items 1, 2, 4, and 5 above, the applicant reported in a submission in February 2008 that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful study to assess this specific issue. We agreed with the applicant regarding the non-feasibility of conducting a meaningful study and concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. In September 2008, we released the applicant from this postmarketing commitment.

For the second Phase 4 study, which addressed item 6 above, based on the reporting of ongoing pregnancies during the first 5 years of Mifeprex distribution, the applicant provided updates in January 2006 and November 2007. Danco reported that only one to two pregnancies per year were followed for final outcomes, and explained that the small number was due, in part, to the requirement that the patients consent to participation after seeking a pregnancy termination. In January 2008, because of the lack of an adequate number of enrolled women, and based on subsequent reports, we released the applicant from this postmarketing commitment.



In addition, as noted in the Mifeprex Approval Memorandum (at 7), we agreed with the Population Council both that it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug and that the pharmacology of mifepristone does not suggest any carryover effect after one-time administration. Accordingly, we did not include item 3 as a Phase 4 commitment in the September 28, 2000, approval letter. However, we note that data from many other studies reported in the medical literature using mifepristone for, e.g., fibroids, uterine myoma, meningioma, psychiatric illnesses, and Cushing's disease, in much higher daily and lower daily doses for chronic use (months) have not raised any major safety issues.<sup>80</sup>

### III. REQUEST FOR STAY AND REVOCATION OF APPROVAL

You request that we immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on your Petition (Petition at 2). You cite 21 CFR 10.35 as the basis for your request for a stay (Petition at 1). In addition, you urge us to revoke the approval of Mifeprex because of the purported legal violations and safety concerns set forth in your Petition (Petition at 2).

As described above, we are denying your Petition. Therefore, your request for a stay pending final action on your Petition is moot.

For the reasons set forth in section II of this response, we conclude that you have not presented any evidence that the applicable grounds in 21 CFR 314.530 have been met with respect to Mifeprex. Furthermore, you have not provided any evidence that any of the applicable grounds in section 505(e) of the FD&C Act have been met for Mifeprex.<sup>81</sup> Therefore, you have not provided any evidence that would serve as a basis for seeking to withdraw the approval of Mifeprex.

---

<sup>80</sup> See, e.g., Tristan, M, et al., 2012, Mifepristone for Uterine Fibroids (Review), Cochrane Library, 8:1-47; Esteve, JL, et al, 2013, Mifepristone Versus Placebo To Treat Uterine Myoma: A Double-Blind, Randomized Clinical Trial, *Int J Womens Health*, 5:361; Spitz, IM, et al., 2005, Management of Patients Receiving Long-Term Treatment With Mifepristone, *Fertil Steril*, 84:1719; Blasey, CM, 1 S Block, JK Belanoff, and RL Roe, 2011, Efficacy and Safety of Mifepristone for the Treatment of Psychotic Depression, *J Clin Psychopharmacol*, 31:436; [Fleseriu, M, et al., 2012, Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome. \*J Clin Endocrinol Metab\*, 97:2039.](#)

<sup>81</sup> You have not presented any clinical data or other information demonstrating that Mifeprex is unsafe for use under its approved conditions for use, either on the basis of evidence available to the Agency at the time of approval or when also considering evidence obtained subsequent to approval. In addition, you have not provided any new evidence that, when evaluated with the evidence available at the time of Mifeprex's approval, shows that there is a lack of substantial evidence that the drug will have its intended effect.

Docket No. FDA-2002-P-0364

#### IV. CONCLUSION

We appreciate and share your concerns about the need to appropriately manage the risks associated with the use of Mifeprex. Our concerns about the potential complications associated with Mifeprex led to its approval in accordance with 21 CFR 314.520. It was deemed to have in effect a REMS in 2007, and it has had an approved REMS since 2011.<sup>82</sup>

For the reasons set forth above, your request that we immediately stay the approval of Mifeprex is moot, and we deny your request that we revoke approval of the Mifeprex NDA. In addition, we deny your request that we conduct an audit of all records of the French and U.S. clinical trials supporting the Mifeprex approval. As with all approved new drug products, we will continue to monitor the safety of Mifeprex and take any appropriate actions.

Sincerely,



Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

---

<sup>82</sup> As of today's approval of Danco's supplemental NDA, the Medication Guide is no longer part of the REMS. However, the Medication Guide will remain as part of approved patient labeling and will be required to be provided to the patient under current Medication Guide regulations.



# Exhibit 30

2011 REMS for NDA 20-687 Mifeprex (mifepristone)  
Tablets, 200mg (June 8, 2011)

NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg

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

## **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

### **I. GOALS**

- 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.

### **II. REMS ELEMENTS**

#### A. Medication Guide

1. A Medication Guide will be dispensed with each MIFEPREX prescription in accordance with 21 CFR 208.24.
2. Please see the appended Medication Guide.

#### B. Elements to Assure Safe Use

1. Healthcare providers who prescribe MIFEPREX will be specially certified.

Danco will ensure that healthcare providers who prescribe MIFEPREX are specially certified.

- a. To become specially certified, each prescriber must complete and fax to the MIFEPREX distributor the one-time Prescriber's Agreement, agreeing that they meet the qualifications and will follow the guidelines outlined in the Prescriber's Agreement.
- b. The following materials are part of the REMS and are appended:
  - i. Prescriber's Agreement.
  - ii. Patient Agreement.



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

Danco will ensure that MIFEPREX will only be available to be dispensed in a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. MIFEPREX will not be distributed to or dispensed through retail pharmacies.

3. MIFEPREX will only be dispensed to patients with documentation of safe use conditions.

Danco will ensure that MIFEPREX will only be dispensed to patients with documentation of the following safe use conditions:

- a. The patient has completed and signed the Patient Agreement, and the Patient Agreement has been placed in the patient's medical record.
- b. The patient has been provided copies of the signed Patient Agreement and the Medication Guide.

C. Implementation System

The Implementation System will include the following:

1. Distributors who distribute MIFEPREX will be certified. To become certified, distributors must agree to:
  - a. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.
  - b. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.
2. Danco will assess the performance of the certified distributors with regard to the following:
  - a. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.
  - b. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.

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

D. Timetable for Submission of Assessments

Danco will submit REMS assessments to the FDA one year from the date of the approval of the REMS and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the assessment reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco will submit each assessment so that it will be received by the FDA on or before the due date.



## MEDICATION GUIDE

**Mifeprex**<sup>®</sup> (MIF-eh-prex)  
(mifepristone)

Read this information carefully before taking Mifeprex\* and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

### What is Mifeprex?

**Mifeprex is used to end an early pregnancy.** It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine misoprostol, 2 days after you take Mifeprex (Day 3), to end your pregnancy. But, about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

### What is the most important information I should know about Mifeprex?

**What symptoms should I be concerned with?** Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases; in most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is \_\_\_\_\_.

#### Be sure to contact your provider promptly if you have any of the following:

**Heavy Bleeding.** Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

**Abdominal Pain or "Feeling Sick".** If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

**Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

**Take this MEDICATION GUIDE with you.** When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that

they understand that you are having a medical abortion with Mifeprex.

**What to do if you are still pregnant after Mifeprex with misoprostol treatment.** If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

**Talk with your provider.** Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

## Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

## How should I take Mifeprex?

- **Day 1 at your provider's office:**
  - Read this MEDICATION GUIDE.
  - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
  - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
  - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
  - This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
  - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.



## **What should I avoid while taking Mifeprex and misoprostol?**

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

## **What are the possible and reasonably likely side effects of Mifeprex?**

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See "How should I take Mifeprex?" for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

## **When should I begin birth control?**

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

\* \* \*

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 3: 4/22/09

\*Mifeprex is a registered trademark of Danco Laboratories, LLC.

MIFEPREX®  
(Mifepristone) Tablets, 200 mg

**PRESCRIBER'S AGREEMENT**

We are pleased that you wish to become a provider of Mifeprex\* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, [www.earlyoptionpill.com](http://www.earlyoptionpill.com).

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.
- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC  
P.O. Box 4816  
New York, NY 10185  
1-877-4 Early Option (1-877-432-7596)  
[www.earlyoptionpill.com](http://www.earlyoptionpill.com)  
\*MIFEPREX is a registered trademark of Danco Laboratories, LLC.



# ACCOUNT SETUP FORM

**MIFEPREX™ (Mifepristone) Tablets, 200 mg; NDC 64875-001-03**

To set up your account:

**1**

Read the Prescriber's Agreement on the back of this Account Setup Form.

**2**

Complete and sign this form.

**3**

Fax the completed Account Setup Form 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 in and are usually shipped within 24 hours.

**6**

Unopened, unused product may be returned for a refund or exchange up to a year after the expiration date.

## 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       Patient Agreements  
 State Abortion Guidelines       Patient Brochures

## 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. Please read the Prescriber's Agreement on the reverse of this form and sign below.

**By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.**

Print Name \_\_\_\_\_ Signature \_\_\_\_\_

Medical License # \_\_\_\_\_ Date \_\_\_\_\_

**Fax this completed Account Setup Form to the authorized distributor. Fax: 1-866-227-3343**

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

\*Mifeprex is a trademark of Danco Laboratories, LLC.



Reference ID: 2957855  
MIFEPREX™  
(Mifepristone) Tablets, 200 mg

EX. 30 pg. 08  
23-10362.684

OWEB

Mifeprex<sup>®</sup> (Mifepristone) Tablets, 200 mg

### **PATIENT AGREEMENT**

Mifeprex\* (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. 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.
14. I will do the following:
  - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
  - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
  - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
  - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
  - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
  - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

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 mifepristone.

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. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05

\*Mifeprex is a registered trademark of Danco Laboratories, LLC.

---

**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)

06/08/2011



# Exhibit 31

2016 FDA Letter to Danco Laboratories re: NDA  
020687, Supp 20 (Mar. 29, 2016)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 020687/S-020

**SUPPLEMENT APPROVAL**

Danco Laboratories, LLC  
(b) (4), (b) (6)

P.O. Box 4816  
New York, NY 10185

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

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

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

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

**APPROVAL & LABELING**

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

**CONTENT OF LABELING**

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

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

Reference ID: 3909592

EX 31 pg. 01  
23-10362.689

**J.A. 284**

The SPL will be accessible from publicly available labeling repositories.

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

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

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

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

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

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

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



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

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

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

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

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

**REMS Assessment Plan**

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

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

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

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

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

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

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

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

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

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

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

**NDA 020687 REMS ASSESSMENT**

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

*or*

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

*or*

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

*or*

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

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

**REMS REVISIONS FOR NDA 020687**

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

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



NDA 020687/S-020  
Page 6

**PROMOTIONAL MATERIALS**

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

**REPORTING REQUIREMENTS**

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

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

Sincerely,

*{See appended electronic signature page}*

[REDACTED] (b) (6)  
[REDACTED]  
Center for Drug Evaluation and Research

NDA 020687/S-020

Page 7

ENCLOSURES:

Content of Labeling

REMS

---

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

---

/s/

---

(b) (6)

03/29/2016



# Exhibit 32

FDA, Center for Drug Evaluation and Research,  
Summary Review of Application Number:  
020687Orig1s020 (March 29, 2016)  
(2016 Summary Review)

**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. <sup>(b) (4)</sup> 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 Mifeprax. 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 Mifeprax 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 Mifeprax 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 Mifeprax orally and 800 mcg of misoprostol buccally 24-48 hours after Mifeprax 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<sup>1</sup>, Boersma et al<sup>2</sup>, Sanhueza Smith et al<sup>3</sup>) and one randomized controlled trial (RCT) (Olavarrieta et al<sup>4</sup>) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin<sup>5</sup> 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<sup>6</sup> 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  $\geq$  800 mcg had a success rate of 96.8%, with an ongoing pregnancy rate of 0.7%.

---

<sup>1</sup> 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

<sup>2</sup> 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

<sup>3</sup> 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

<sup>4</sup> Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousiequez 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

<sup>5</sup> Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion *Obstet Gynecol*: a Systematic Review. *Obstet Gynecol* 2015; 126(1): 12-21

<sup>6</sup> 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<sup>7</sup> 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<sup>8</sup> 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<sup>9</sup>) 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:

---

<sup>7</sup> Wedisinghe L and Elsandabese 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

<sup>8</sup> 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

<sup>9</sup> 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<sup>10</sup> – 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<sup>11</sup> – 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<sup>12</sup> – 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<sup>13</sup> – 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<sup>14</sup> – 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<sup>15</sup> – 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

---

<sup>10</sup> 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

<sup>11</sup> 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

<sup>12</sup> 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

<sup>13</sup> 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

<sup>14</sup> 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

<sup>15</sup> 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<sup>16</sup>. 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 proposed 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<sup>17</sup> 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)

(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.

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

<sup>17</sup>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<sup>18</sup>) explicitly addressed deaths and noted that there were no deaths among 578 subjects evaluated in the study. Only one observational study (Goldstone, et al<sup>19</sup>) 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

<sup>18</sup>Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.

<sup>19</sup>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<sup>20</sup> 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<sup>21</sup>) 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)<sup>22</sup> 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<sup>23</sup>) to 22% in the Grossman et al<sup>24</sup> study using telemedicine to deliver medical

<sup>20</sup>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.

<sup>21</sup>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.

<sup>22</sup>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.

<sup>23</sup>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.

<sup>24</sup>Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through 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 ( $\geq 15\%$ ) 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<sup>25</sup>, Winikoff<sup>26</sup> and Winikoff<sup>27</sup> 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<sup>28</sup> and Gatter et al<sup>29</sup>) 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.

<sup>25</sup> 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

<sup>26</sup> 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

<sup>27</sup> 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

<sup>28</sup> 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.

<sup>29</sup> 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<sup>30,31,32</sup> 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

---

<sup>30</sup>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

<sup>31</sup>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

<sup>32</sup>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 Mifeprax 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<sup>33</sup>. 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<sup>34</sup> and Ireland et al<sup>35</sup>. 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<sup>36</sup>) 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

---

<sup>33</sup> 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.

<sup>34</sup> 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.

<sup>35</sup> 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.

<sup>36</sup> 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<sup>37</sup> 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<sup>38</sup> 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<sup>39</sup> 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

---

<sup>37</sup> 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.

<sup>38</sup> 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.

<sup>39</sup> 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<sup>40</sup>) 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  $\geq 96\%$  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.

---

<sup>40</sup> 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<sup>41</sup>). 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<sup>42</sup>)**

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<sup>43</sup> 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<sup>44</sup> 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<sup>45</sup> evaluated data from 28 adolescents aged 14 to 17, at  $\leq 56$  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.

<sup>41</sup>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.

<sup>42</sup> Ibid.

<sup>43</sup>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.

<sup>44</sup>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.

<sup>45</sup>Phelps RH, et al. Mifepristone abortion in minors. *Contraception* 2001;64:339-343.

- Niinimaki et al<sup>46</sup> used data from a Finnish Registry from 2000-2006. An analysis of efficacy between adolescents under age 18 compared to the women  $\geq$  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<sup>47</sup> 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)

(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

<sup>46</sup>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.

<sup>47</sup>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.

<sup>48</sup>Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. *BJM* 2011;342: d2111.



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

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

(b) (6) reviewed the Prescribing Information (PI) in addition to the joint review with (b) (6) of the Medication Guide in conjunction with (b) (6). After review, (b) (6) provided recommended changes (See (b) (6) review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in the PI and incorporated appropriate changes into the final label.

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

(b) (6) (b) (6) in the (b) (6) (b) (6) reviewed the proposed modifications to the REMS. The (b) (6) review reflected agreement with the Applicant's proposed REMS changes which include:

- Removal of the term “under Federal law” from the Prescriber’s Agreement.
- Replacement of the word “physician” with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex. (b) (6) believes that the Applicant’s proposed terminology of “(b) (4)” is too broad and that a more appropriate description is “healthcare provider who prescribes,” which limits acceptable healthcare providers to those who are licensed in their state to prescribe medications.
- Removal of the Medication Guide from the REMS. The Medication Guide remains an important education tool for patients. It will still be dispensed to each patient in accordance with 21 CFR part 208. As described in the Medication Guide Guidance, a Medication Guide is not necessary to ensure that the benefits outweigh the risks of Mifeprex.
- Modification of Element to Assure Safe Use (ETASU) A, the Prescriber’s Agreement. (b) (6) recommends changing the name of the document to the Prescriber’s Agreement Form to be consistent with other REMS programs. References to “physician” should be changed to “healthcare provider who prescribes.”
- (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
  1. The established safety profile over 15 years of experience with Mifeprex is well-characterized, stable, and known serious risks occur rarely
  2. The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208
  3. The Prescriber’s Agreement Form will continue to require providers to explain the treatment, its effects and risks associated with Mifeprex and to answer any questions that a patient may have
  4. Established clinical practice provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment. FDA has removed REMS

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

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

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

## 12. Labeling

Carton and container labeling was reviewed by the (b) (6) (b) (6) (b) (6) (b) (6) and the (b) (6) (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 Mifeprax 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 Mifeprax, includes counseling on all options for termination of pregnancy, access to pain management and emergency services if needed.
- Medical abortion with Mifeprax 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 Mifeprax be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprax 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 Mifeprax REMS program will have a modified ETASU REMS that will continue to ensure that Mifeprax 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 Mifeprax REMS program will continue to ensure that the modified Mifeprax 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) [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 the [REDACTED] (b) (6) [REDACTED] (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

# Exhibit 35

2019 Citizen Petition of Am. Ass'n of Pro-Life  
Obstetricians & Gynecologists to FDA (Mar. 29, 2019)



## Citizen Petition

March 29, 2019

The undersigned submit this petition to request the Commissioner of Food and Drugs to: (I) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (II) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS), and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

### A. Action Requested

#### I. RESTORE AND STRENGTHEN ELEMENTS OF THE MIFEPREX REGIMEN AND PRESCRIBER REQUIREMENTS APPROVED IN 2000.

Current language and requested language for the Mifeprex Label and the Mifeprex *Risk Evaluation and Mitigation Strategy* (REMS) are included in Exhibit A.<sup>1</sup> Requests include:

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

#### B. Dosage and Administration.

1. Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.
2. The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

**C. Contraindications.** Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

**D. Adverse Event Reporting.** Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

---

<sup>1</sup> Other documents will require corresponding modifications, including the Mifeprex Medication Guide, Prescriber Agreement Form, and Patient Agreement Form.

**E. Additional studies.** The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

**II. RETAIN THE MIFEPREX RISK EVALUATION AND MITIGATION STRATEGY (REMS), AND CONTINUE LIMITING THE DISPENSING OF MIFEPREX TO PATIENTS IN CLINICS, MEDICAL OFFICES, AND HOSPITALS, BY OR UNDER THE SUPERVISION OF A CERTIFIED PRESCRIBER.**

**A. Retain the Mifeprex REMS.**

**B. Continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.**

1. Mifeprex should be dispensed only in clinics, medical offices, and hospitals.

**a. The “TelAbortion” Direct-to-Consumer Mifeprex Study**

**b. The Mifeprex through Pharmacy Dispensing Study**

**c. Beyond the Current Studies**

2. Mifeprex Prescribers Should be Certified.

## B. Statement of Grounds

### I. RESTORE AND STRENGTHEN ELEMENTS OF THE MIFEPREX REGIMEN AND PRESCRIBER REQUIREMENTS APPROVED IN 2000.<sup>2</sup>

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

In 2016, FDA increased the maximum gestational age for Mifeprex use for abortion from 49 days (7 weeks) to 70 days (10 weeks), and changed the method of administration of misoprostol from oral to buccal (*i.e.*, in the cheek pouch). However drug-induced abortion<sup>3</sup> regimens demonstrate an increase in complications and failures after 49 days' gestation.

In a 2011 study of thousands of patients, the majority of whom had a drug-induced abortion using what is now the Mifeprex regimen, the rate of infection and the rate of failure requiring surgical intervention increased with gestational age.<sup>4</sup> The American College of Obstetricians and Gynecologists (ACOG) has stated: "the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days."<sup>5</sup>

Further, a 2015 meta-analysis examined all the existing publications on buccal administration of misoprostol, 20 studies in all, from November 2005 through January 2015. The failure rate of the buccal misoprostol regimen increased as the gestational age

---

<sup>2</sup> The FDA approved Mifeprex for use in the United States on September 28, 2000, with safeguards considered necessary to ensure patient safety. The drug's initial approval was for termination of pregnancy, in a regimen with misoprostol, through 49 days of pregnancy. FDA significantly modified the drug's label at the application of the manufacturer, Danco Laboratories, in 2016, extending approved use to 70 days of pregnancy. Additional changes included: a new dosage of both Mifeprex and misoprostol; permitting home administration of Mifeprex and misoprostol; a new route of administration for the misoprostol (buccal, in the cheek pouch); permitting non-physicians to become certified prescribers; a decrease from 3 to 1 mandatory office visits by the patient; and reduced reporting requirements. U.S. Gov't Accountability Office, GAO-18-292, Food and Drug Administration: Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts 4-7 (2018); Mifeprex Risk Evaluation and Mitigation Strategy (REMS), [https://www.accessdata.fda.gov/drugsatfda\\_docs/remms/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remms/Mifeprex_2016-03-29_REMS_full.pdf); Mifeprex Medication Guide, <https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf>.

<sup>3</sup> The terms "Medication abortion," "medical abortion," "chemical abortion," and "drug-induced abortion" [or termination of pregnancy] share the same meaning and refer to the use of abortion-inducing drugs, rather than surgery, to induce abortion. The current FDA-approved regimen uses two drugs, mifepristone (a.k.a. Mifeprex or RU-486) and misoprostol.

<sup>4</sup> Mentula MJ, Niinimäki M, Suhonen S, Hemminki E, Gissler M, and Heikinheimo O, *Immediate Adverse Events after Second Trimester Medical Termination of Pregnancy: Results of a Nationwide Registry Study*, Human Reproduction 26(4), 927-932 (2011).

<sup>5</sup> ACOG Practice Bulletin 143: *Medical Management of First-Trimester Abortion*, p. 5 (Mar. 2014, reaffirmed 2016).



increased, especially at gestational ages greater than 49 days.<sup>6</sup> The current FDA label also acknowledges this fact.<sup>7</sup>

Given the serious risks of failure, hemorrhage, infection, and ongoing pregnancy that increase as pregnancy advances, the gestational limit for the Mifeprex regimen should have never been increased.

## **B. Dosage and Administration.**

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

The 2000 Mifeprex regimen required Mifeprex to be “provided by or under the supervision of a *physician*” who meets qualifications discussed in this section below.<sup>8</sup> However, the 2016 regimen replaced “physician” with “healthcare provider,” thus permitting non-physicians to apply to be certified prescribers.<sup>9</sup> Given the regimen’s serious risks, the FDA should limit the ability to prescribe and dispense Mifeprex to qualified, licensed physicians. Physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age.

The current Mifeprex Risk Evaluation and Mitigation Strategy (REMS), discussed in Section II below, continues to provide that “Mifeprex must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, *by or under the supervision of a certified prescriber.*”<sup>10</sup> Yet, abortion providers today are promoting and performing “telemedicine abortions,” where the certified prescriber’s “supervision” of the dispensing of Mifeprex is limited to a videoconference.<sup>11</sup> This practice demonstrates a flagrant disregard for FDA safeguards.

To ensure true supervision, the FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex. This requirement would be consistent with other requirements in the Mifeprex Label and REMS.

---

<sup>6</sup> Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, *Obstet. Gynecol* 126 (1) July 2015 12-21.

<sup>7</sup> Mifeprex 2016 label, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf).

<sup>8</sup> Mifeprex 2000 label, Dosage and Administration, emphasis added.

<sup>9</sup> Mifeprex 2016 label, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf).

<sup>10</sup> Mifeprex 2016 REMS, emphasis added,

[https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf).

<sup>11</sup> See Planned Parenthood Releases New Educational Video on Telemedicine Abortion (Feb. 6, 2018), <https://www.plannedparenthood.org/about-us/newsroom/press-releases/planned-parenthood-releases-new-educational-video-on-telemedicine-abortion>.

In the Mifeprex Label, the FDA emphasizes that “Mifeprex is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)” because of the drug’s “risks of serious complications.” In a bold-print box, the FDA states that before prescribing Mifeprex, a provider must inform a patient: about the risks of serious events; whom to call and what to do if certain symptoms occur; and to take the Medication Guide with her if she visits an emergency room or healthcare provider who did not prescribe Mifeprex, so that she receives appropriate, informed care.<sup>12</sup>

Further, a provider must sign a Provider Agreement Form, attesting that he or she can:

- **Assess the duration of pregnancy accurately.**<sup>13</sup> Failures and complications of Mifeprex abortion increase with increasing gestational age. Mifeprex use is approved through 70 days’ gestation.<sup>14</sup> FDA should strengthen this requirement by mandating that gestational age be accurately assessed by ultrasound in order to both ensure compliance with FDA restrictions and adequately inform the patient of gestational age-specific risks, which rise with increasing gestational age.
- **Diagnose ectopic pregnancies**<sup>15</sup> (*i.e.*, extrauterine pregnancy; pregnancy outside the uterus), which Mifeprex cannot end. When an ectopic pregnancy progresses, it can rupture the fallopian tube, causing bleeding, severe pain, or death. If a woman with an extrauterine pregnancy is given Mifeprex, she may believe the symptoms for ectopic pregnancy are simply the side effects of drug-induced abortion, which are similar. As of December 31, 2017, at least 97 women with ectopic pregnancies in the United States had been given Mifeprex.<sup>16</sup> Of these women, at least two bled to death from an undiagnosed ectopic pregnancy.<sup>17</sup> They likely did not recognize that their cramps, abdominal pain, and perhaps vaginal bleeding were dangerous—not side effects expected in a Mifeprex abortion.<sup>18</sup>

---

<sup>12</sup> Mifeprex 2016 label, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s0201b1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s0201b1.pdf).

<sup>13</sup> Mifeprex Prescriber Agreement Form, [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_Prescriber\\_Agreement\\_Form.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf).

<sup>14</sup> See Section I.A, *supra*.

<sup>15</sup> Mifeprex Prescriber Agreement Form, [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_Prescriber\\_Agreement\\_Form.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf).

<sup>16</sup> Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2017, RCM # 2007-525, NDA 20-687, <https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM603000.pdf>.

<sup>17</sup> *Id.*

<sup>18</sup> Donna Harrison, M.D. & Michael J. Norton Testimony before the Iowa Board of Medicine, p. 3 (Aug. 21, 2013), *citing* Postmarket Drug Safety Information for Patients and Providers, Questions and Answers on Mifeprex,

- **Provide surgical intervention if needed, or has made plans to provide such care through others.**<sup>19</sup> He or she must assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.<sup>20</sup>

Clearly, a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional contraindications (*i.e.*, circumstances that make a treatment or medication *unadvisable*) to Mifeprex use. These physical contraindications include pelvic infections, ovarian masses, cardiac arrhythmias, and liver abnormalities.<sup>21</sup> A physician bears responsibility to diagnose and rule out contraindications prior to Mifeprex use. It is inadequate to entrust this critical care to another healthcare provider who is not trained in diagnosis. Further, a healthcare provider who is not physically accessible to a patient cannot provide adequate follow-up care to patients, as required by the FDA Mifeprex regimen.

Thirty-four states permit only physicians to prescribe Mifeprex,<sup>22</sup> with nineteen states requiring the provider to be physically present with the patient.<sup>23</sup> For example, the law in Alabama states that the physical presence and care of a physician are necessary because “the failure and complications from medical abortion increase with advancing gestational age, because the physical symptoms of medical abortion can be identical to the symptoms of ectopic pregnancy, and because abortion-inducing drugs do not treat ectopic pregnancies but rather are contraindicated in ectopic pregnancies.”<sup>24</sup>

Lawmakers in these states recognize that abortion providers cannot diagnose contraindications and cannot adequately care for their patients through a videoconference. Fundamentally, telemedicine “may be legitimate when it comes to discrete, document-based tasks such as reading X-rays,” but it “is not the standard of care when it comes to abortion or the management of miscarriage.”<sup>25</sup>

---

<https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm492705.htm>.

<sup>19</sup> Mifeprex Prescriber Agreement Form,

[https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf)

[29\\_Prescriber\\_Agreement\\_Form.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf).

<sup>20</sup> *Id.*

<sup>21</sup> Harrison & Norton Testimony, p. 3.

<sup>22</sup> Donovan MK, *Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care*, Guttmacher Policy Review, Vol. 21, p. 44 (2018).

<sup>23</sup> *Id.*

<sup>24</sup> Ala. Code § 26-23E-7.

<sup>25</sup> Harrison & Morton Testimony, p. 19.



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

The 2016 regimen significantly diminished doctor-patient interaction. While the 2000 Mifeprex label required three patient visits with the abortion provider, women may now obtain Mifeprex at a clinic and self-administer it at home. They are no longer required to return to the clinic for the administration of misoprostol, which prevents abortion providers from ensuring that they take the drugs at the correct times. Further, providers may now “confirm” that a patient’s drug-induced abortion was successful without a clinic visit,<sup>26</sup> increasing the threat that Rh-negative patients will not receive administration of Rhogam, which is necessary to prevent serious risks in subsequent pregnancies.

The 2016 regimen directs that patients be given or prescribed misoprostol to take 24 to 48 hours after taking Mifeprex. However, without monitoring, a patient may take misoprostol before 24 hours have passed since she consumed Mifeprex, rendering the regimen ineffective and increasing the likelihood that she will experience a failed drug-induced abortion and require surgery.

Using buccal misoprostol sooner than 24 hours after administering mifepristone leads to a significantly increased failure rate. In one study investigating the timing of buccal misoprostol after mifepristone, nearly one out of every three to four women who took buccal misoprostol shortly after mifepristone failed to abort.<sup>27</sup> The failure rate ranged from 27% to 31%, depending on the pregnancy gestation.<sup>28</sup> Given these results, the authors of this study strongly recommended that buccal misoprostol not be taken immediately after mifepristone because of the very high abortion failure rate.<sup>29</sup> However, with home administration of misoprostol, healthcare providers have no control over when their patients consume the drug.

A woman may also choose to swallow misoprostol rather than keep the pill between her cheek and gum for 30 minutes, converting a “buccal” administration into an “oral” administration. An oral administration of misoprostol following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy.

Further, waiting until 24 hours after Mifeprex to administer misoprostol does not guarantee success, and the failure rate of buccal misoprostol is higher than that under the 2000 regimen. A comprehensive systematic review and meta-analysis of the existing

---

<sup>26</sup> See Mifeprex 2016 label,

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s0201b1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s0201b1.pdf).

<sup>27</sup> Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD, *Oral Mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study*, *Contraception* 76 (2007) 215-220.

<sup>28</sup> *Id.*

<sup>29</sup> *Id.*

studies of the 2016 regimen found that women who take misoprostol earlier than 48 hours after mifepristone are more likely to fail the regimen.<sup>30</sup>

Under the 2000 regimen, doctors were also able to provide care to patients during the most challenging and painful time in the drug-induced abortion. According to the World Health Organization, up to 90% of women will abort within 4-6 hours after taking misoprostol.<sup>31</sup> The 2000 regimen permitted a patient to be in a clinic for this period of time, during which she would be under the observation and care of medical personnel. This observation period is for “both patient safety and compassion. . . . This is the time when women should be in a place where their bleeding can be monitored, their vital signs can be observed by trained medical personnel, and they can receive sufficient pain medication during the most difficult part of the expulsion.”<sup>32</sup>

Abortion complications are also more frequent when women abort at home, without the oversight of a healthcare provider. A 2018 combined retrospective and longitudinal follow-up study of complications related to induced abortion in Sweden determined that “[t]he complication frequency [of drug-induced abortion] was significantly higher among women <7 gestational weeks who had their abortions *at home*.”<sup>33</sup>

In-person contact with a healthcare provider is critical to post-abortion care as well. Abortion providers should perform a “follow-up [physical exam] after the use of mifepristone in order to confirm abortion and rule out life-threatening infection.”<sup>34</sup> Before FDA approved the 2016 regimen, the follow-up visit was considered “very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.”<sup>35</sup> In fact, the 2000 label provided that “[e]ach patient must understand the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex.”<sup>36</sup> ACOG’s current policy explains that:

Women are not good candidates for medical abortion if they ... desire quick completion of the abortion process [or] are not available for follow-up contact or evaluation....<sup>37</sup>

<sup>30</sup> Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, *Obstet.Gynecol* 126 (1) July 2015 12-21.

<sup>31</sup> World Health Organization, *Safe Abortion: Technical and Policy Guidance for Health Systems* 45.

<sup>32</sup> Donna Harrison, M.D., *Aff. Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015) ¶ 136.

<sup>33</sup> Carlsson I, Breeding K, and Larsson PG, *Complications Related to Induced Abortion: a Combined Retrospective and Longitudinal Follow-up Study*, *BMC Women’s Health* (2018) 18:158, p. 4 (emphasis added).

<sup>34</sup> Harrison & Norton Testimony, p. 18.

<sup>35</sup> Mifeprex 2000 label, Day 14: Post-Treatment Examination.

<sup>36</sup> Mifeprex 2000 label, Information for Patients.

<sup>37</sup> ACOG Practice Bulletin 143, p. 6.

In addition to ensuring for all drug-induced abortion patients that the uterus has been emptied of retained tissue and that they are not suffering from infection, the follow-up examination is particularly critical for Rh-negative patients. These patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without follow-up, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies.<sup>38</sup>

Nonetheless, abortion advocates strongly supported the reduction in required visits, and continue to advocate for the elimination of direct provider-patient contact. Gynuity Health Projects (an organization that “has been at the forefront of efforts to increase women’s access to medical abortion in settings throughout the world”)<sup>39</sup> has conducted at least three domestic and five international studies<sup>40</sup> on eliminating pelvic ultrasound or exam after drug-induced abortion. Following one study, researchers determined that “[s]emi-quantitative pregnancy tests ... could be used in lieu of transvaginal ultrasound and/or serum hCG at clinic-based follow-up or by women themselves for home-based follow-up.”<sup>41</sup>

In a more recent study, researchers asserted that the “common practice of scheduling a clinical contact after every medical abortion may not be necessary to ensure safety; enabling patients to determine for themselves whether or not a contact is needed can be a

<sup>38</sup> ACOG Practice Bulletin 181: *Prevention of Rh D Alloimmunization* (Aug. 2017); and SOGC Clinical Practice Guidelines: *Prevention of Rh Alloimmunization* (No. 133, Sept. 2003).

<sup>39</sup> See Gynuity Health Projects, Medical Abortion, <https://gynuity.org/programs/medical-abortion>. Founded by Beverly Winikoff, M.D., M.P.H., in 2003, Gynuity outlines on its “Medical Abortion” page the organization’s research projects, including efforts to: “Develop innovative service delivery systems through telemedicine; Simplify and de-medicalize medical abortion services; Expand access to medical abortion in the 1<sup>st</sup> and 2<sup>nd</sup> trimesters of pregnancy; Conduct clinical research to develop new abortion medications; Develop a ‘missed menses pill’/menstrual regulation method; Develop additional clinical indications for mifepristone.” Gynuity has launched a “coalition to expand access to mifepristone in the United States,” co-created a “medical abortion commodities database,” “introduce[d] medical abortion in new settings,” “incorporate[ed] new clinical evidence into service guidelines,” and “expanded medical abortion access through education and local champions.”

<sup>40</sup> See, e.g., *Self-Assessment of Medical Abortion Outcome Using Serial Multi-level Pregnancy Tests* [NCT02570204] (Sept. 2015 – Dec. 2016), <https://www.clinicaltrials.gov/ct2/show/NCT02570204?term=Self-Assessment+of+Medical+Abortion+Outcome+Using+Serial+Multi-level+Pregnancy&rank=1>; *Exploring the Role of At-home Semi-Quantitative Pregnancy Tests for Medical Abortion Follow-up* [NCT01150279] (Aug. 2009 – May 2014), <https://www.clinicaltrials.gov/ct2/show/NCT01150279?term=Exploring+the+Role+of+At-home+Semi-Quantitative+Pregnancy+Tests+for+Medical+Abortion+Follow-up&rank=1>; *De-Medicalizing Mifepristone Medical Abortion* [NCT00120224] (May 2005 – Apr. 2007), <https://www.clinicaltrials.gov/ct2/show/NCT00120224?term=De-Medicalizing+Mifepristone+Medical+Abortion&rank=1>.

<sup>41</sup> Lynd K, et al., *Simplified Medical Abortion Using a Semi-Quantitative Pregnancy Test for Home-Based Follow-up*, *Int J Gynaecol Obstet*. 2013 May;121(2):144-8.



reasonable approach.”<sup>42</sup> They reached this conclusion even with 26% of participants failing to provide sufficient follow-up information.<sup>43</sup>

Gynuity researchers also conducted a recent systematic review of existing studies on “the accuracy and acceptability of a strategy for identifying ongoing pregnancy after medical abortion treatment using a low-sensitivity pregnancy test (LSPT).” While the researchers acknowledged that “the LSPT strategy had *moderate* sensitivity for identifying ongoing pregnancy” and “the LSPT itself had a limited role in the detection of treatment failures [*i.e.*, ongoing pregnancy] in the studies,” they stated that the “LSPT strategy shows promise for reducing the need for in-person follow-up after medical abortion. A range of home-based options should be validated to meet the varied needs of women and abortion providers in diverse settings.”<sup>44</sup>

In reality, a de-emphasis on follow-up care increases risks of post-abortion complications. As discussed above, the 2000 regimen’s requirement that women return approximately 14 days after ingesting mifepristone was considered necessary to ensure that all pregnancy tissue had been passed.<sup>45</sup> This determination is crucial, because retained pregnancy tissue can lead to continued bleeding and serious intrauterine infections. The return visit permits healthcare providers to ensure that a patient is not experiencing these or other complications from the abortion procedure, and that Rh negative patients are administered Rhogam to protect future pregnancies.

Abortion advocates argue that three clinic visits make accessing abortion-inducing drugs more difficult for patients with transportation challenges; however, as noted above, ACOG acknowledges that drug-induced abortion is *contraindicated* for patients who “are not available for follow-up contact or evaluation.”<sup>46</sup> Surgical abortion is a better choice for these patients, because it “[d]oes not require follow-up in most cases.”<sup>47</sup>

Drug-induced abortion is a longer process that requires more attention and care from healthcare providers. Three visits to a physician in the interest of patient safety should not be sacrificed for the convenience of healthcare providers or even their patients.

---

<sup>42</sup> Raymond EG, et al., *Self-assessment of Medical Abortion Outcome Using Symptoms and Home Pregnancy Tests*, *Contraception* 97 (2018) 324-28.

<sup>43</sup> *Id.*

<sup>44</sup> Raymond EG, et al., *Low-sensitivity Urine Pregnancy Testing to Assess Medical Abortion Outcome: A Systematic Review*, *Contraception* (2018), <https://doi.org/10.1016/j.contraception.2018.03.013> (emphasis added).

<sup>45</sup> Mifeprex 2000 label, Day 14: Post-Treatment Examination.

<sup>46</sup> ACOG Practice Bulletin 143, p. 6.

<sup>47</sup> *Id.*

**C. Contraindications.** Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

The 2000 Mifeprex Label stated:

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.<sup>48</sup>

This critical language was excluded from the 2016 Mifeprex Label. Yet, studies comparing the outcome of surgical versus drug-induced abortion “have clearly demonstrated that Mifeprex abortions have a greater risk of hemorrhage, infection, continued pregnancies, retained tissue and need for emergency reoperation than surgical abortions.”<sup>49</sup> ACOG acknowledges that “[c]ompared with surgical abortion, medical abortion takes longer to complete, requires more active patient participation, and is associated with higher reported rates of bleeding and cramping,” and has lower success rates.<sup>50</sup>

Drug-induced abortion is optional. If a woman does not meet the criteria necessary to use abortion-inducing drugs, then surgical abortion is still an option. For women with transportation difficulties, an abortion provider can complete surgical abortion “in a predictable period of time,” and the procedure “[d]oes not require follow-up in most cases.”<sup>51</sup>

Efforts to promote abortion-inducing drugs to women in rural areas where access to emergency medical care is scarce are detrimental to women’s health. It is better for a patient in a remote region to have a surgical abortion, “which requires a single visit, and is less likely to result in serious or life-threatening complications.”<sup>52</sup>

---

<sup>48</sup> Mifeprex 2000 label, Contraindications.

<sup>49</sup> Harrison Aff. ¶ 115.

<sup>50</sup> ACOG Practice Bulletin 143, p. 3 & Box 1.

<sup>51</sup> *Id.*

<sup>52</sup> Harrison & Norton p. 9.

**D. Adverse Event Reporting.** Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

The 2016 regimen dramatically reduced accountability for Mifeprex providers by limiting adverse event reporting (AER) requirements, a critical safety mechanism.<sup>53</sup> While prescribers were required to report any serious adverse event associated with Mifeprex under the 2000 label, they are now required to report only deaths associated with Mifeprex.

Even with the 2000 regimen requirements, collecting accurate and complete adverse event information was highly difficult. Adverse events were often not reported or were interpreted by emergency health care providers as the results of spontaneous abortion.<sup>54</sup> The Mifeprex label instructs prescribers to “[a]dvice the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe Mifeprex, so that the provider knows that she is undergoing a medical abortion.”<sup>55</sup> Yet, many Mifeprex prescribers violate FDA protocol, instructing their patients to lie to emergency medical personnel. The organization Aid Access instructs patients that if they need to go to an emergency room:

You do not have to tell the medical staff that you tried to induce an abortion; you can tell them that you had a spontaneous miscarriage. Doctors have the obligation to help in all cases and know how to handle a miscarriage. The symptoms of a miscarriage and an abortion with pills are exactly the same and the doctor will not be able to see or test for any evidence of an abortion, as long as the pills have completely dissolved.<sup>56</sup>

Such deception prevents emergency healthcare providers from appropriately caring for their patients, and further decreases the likelihood that adverse events will be reported.

With reduced AER reporting requirements under the 2016 label, what was previously difficult is now virtually impossible. The FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events. AERs are the only objective means by which FDA has any data whatsoever on the effects of the

---

<sup>53</sup> Mifeprex 2016 label.

<sup>54</sup> See GAO-18-292, pp 24-25.

<sup>55</sup> Mifeprex 2016 label, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s0201b1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s0201b1.pdf).

<sup>56</sup> Aid Access, *How do you know if you have complications, and what should you do?*, <https://aidaccess.org/en/page/459/how-do-you-know-if-you-have-complications-and-what-should-you-do>.



Mifeprex regimen on women, and the voluntary and minimal nature of the current AERs means that FDA has no accurate information about the actual number of women injured by drug-induced abortion, or the nature of complications caused by this drug.

After prescribing Mifeprex and misoprostol, certified prescribers should at minimum be required to report the following directly to the FDA Medwatch reporting system, copying Danco Laboratories: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications. Detailed information must also be included, such as pulse, blood pressure, temperature, pre- and post-transfusion hemoglobin/hematocrit, white blood count, number of units of blood transfused, surgeries, and any other pertinent laboratory or hospital course information, as well as emergency room and hospital discharge diagnoses.

Further, FDA should provide guidance to emergency healthcare providers and physicians responsible for treating complications so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage. The guidance should also instruct these providers on how to report adverse events.<sup>57</sup>

The abysmal quality of the current AERs received from Danco Laboratories shows the lack of concern that Danco has demonstrated for the safety of the women who have undergone drug-induced abortion. Responsible reporting is a fundamental safety mechanism that should not be sacrificed in the interest of convenience for abortion providers.

**E. Additional Studies.** The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

Mifeprex was approved for use in the pediatric population in 2000 after the FDA waived, without explanation, the requirement for studies in the pediatric population. The developmental stage of puberty involves a complex interplay of both progesterone and estrogen effects on the developing female reproductive system. The use, and especially the potential multiple use, of Mifeprex, which is a powerful progesterone blocker, is

---

<sup>57</sup> The Self-Induced Abortion Legal Team has created a document titled “Self-Induced Abortion and the Law: What Emergency Room Staff Need to Know.” This document heavily emphasizes patient privacy requirements, including the penalties that healthcare providers may face if they disclose patient information. While these concerns are valid, emergency healthcare providers should also have training on public health reporting requirements and how such reporting does not violate HIPAA or other laws regarding patient privacy. *See*, <https://www.sialelegalteam.org>.

likely to significantly impact the developing reproductive system of the adolescent female.<sup>58</sup> It is irresponsible to allow the continued uninvestigated use of Mifeprex in the pediatric female population<sup>59</sup> without requiring long-term studies on the impact of Mifeprex use on pubertal development.

More than one out of every three abortions in the U.S. is a repeat abortion.<sup>60</sup> The repeat use of Mifeprex has been associated in some studies with adverse reproductive health outcomes in future wanted pregnancies.<sup>61</sup> This concern requires further study.

The adverse events of hemorrhage, retained tissue, and infection are common after Mifeprex use. The hemorrhage is often significant enough to warrant transfusion. When patients lack access to emergency medical facilities, such complications could easily translate to deaths. Thus a study of deaths and of severe hemorrhages requiring transfusion should be done to compare outcomes in women with and without access to emergency medical facilities.

**II. RETAIN THE MIFEPREX RISK EVALUATION AND MITIGATION STRATEGY (REMS), AND CONTINUE LIMITING THE DISPENSING OF MIFEPREX TO PATIENTS IN CLINICS, MEDICAL OFFICES, AND HOSPITALS, BY OR UNDER THE SUPERVISION OF A CERTIFIED PRESCRIBER.**

**A. Retain the Mifeprex REMS.**

Mifeprex, when used for abortion, is subject to a Food and Drug Administration (FDA) *Risk Evaluation and Mitigation Strategy* (REMS) with *elements to assure safe use* (ETASU). FDA determined that the Mifeprex REMS is necessary to ensure the safety and efficacy of the drug, because it carries risks of life-threatening hemorrhage, infection, continued pregnancy, retained tissue, need for emergency surgery, and death. The approved Mifeprex regimen includes the use of another potent drug, misoprostol, which carries its own risks.

Under the Mifeprex REMS with ETASU, a healthcare provider must be certified to prescribe Mifeprex by reviewing the prescribing information and completing a

---

<sup>58</sup> Arain M, et al., *Maturation of the adolescent brain*, *Neuropsychiatric Disease and Treatment*, 2013:9 449-461.

<sup>59</sup> Because of their immaturity, minors are also less likely to understand the importance of following prescriber instruction or of recognizing when they need to seek emergency medical treatment.

<sup>60</sup> Jones R, et al., *Which Abortion Patients Have Had a Prior Abortion? Findings from the 2014 U.S. Abortion Patient Survey*, *Journal of Women's Health*, DOI: 10.1089/jwh.2017.6410 (2014).

<sup>61</sup> Fang L, et al., *Repeated Abortion Affects Subsequent Pregnancy Outcomes in BALB/c Mice*, *PLoS ONE* 7(10): e48384. doi:10.1371/journal.pone.0048384 (2012).

“Prescriber Agreement Form,” attesting that they can: assess the duration of pregnancy accurately; diagnose ectopic pregnancies; and provide surgical intervention in cases of incomplete abortion or severe bleeding, or designate someone else to provide that care. Further, they must agree to follow the guidelines for use of Mifeprex.

The REMS also requires Mifeprex to “be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.” Mifeprex may not be distributed or dispensed through retail pharmacies. Also, a patient must sign a “Patient Agreement Form” and be fully informed of the risks by a certified prescriber. She must receive the Mifeprex Medication Guide, informing her that she needs a “follow-up assessment” 7 to 14 days after she has taken Mifeprex to ensure that she is well and has terminated her pregnancy.<sup>62</sup>

The REMS remains the lone safeguard to monitor and mitigate the risks of death and adverse events from the Mifeprex regimen. Gynuity Health Projects and researchers from the University of California, San Francisco (UCSF) obtained approval from FDA through Investigational New Drug Applications (INDs) to conduct studies that *do not* comply with the Mifeprex REMS. They intend to use the results of these studies to press for the elimination of the Mifeprex REMS.<sup>63</sup> [See Section II.B, below.]

The Mifeprex Medication Guide acknowledges that serious risks accompany FDA’s approved regimen for drug-induced abortion, which includes the use of Mifeprex and another potent drug, misoprostol. The document improperly downplays the risks, however, stating that “*rarely*, serious and potentially life-threatening bleeding, infections, or other problems can occur following . . . medical abortion.” Specifically, “in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure.”<sup>64</sup>

In fact, the internationally used criteria for reporting complications from drugs demonstrate that complications from drug-induced abortions are common, not rare. The Council for International Organizations of Medical Sciences (CIOMS)<sup>65</sup> defines the word

---

<sup>62</sup> GAO-18-292, pp 4-7 (2018); Mifeprex Risk Evaluation and Mitigation Strategy (REMS), [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf); 21 U.S.C. § 355-1; Mifeprex Medication Guide, <https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf>.

<sup>63</sup> See Daniel Grossman, MD, Research Protocol: *Alternative Provision of Medication Abortion via Pharmacy Dispensing*, Version #:1.3 (July 17, 2018) p. 14.

<sup>64</sup> Mifeprex Medication Guide, <https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf>.

<sup>65</sup> The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, nonprofit organization established jointly by WHO and UNESCO in 1949. Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. In 2013, the membership of CIOMS included 49 international, national, and associate member organizations, representing many of the biomedical disciplines, national academies of sciences, and medical research councils.



“rare” in adverse event reporting as an event that happens in between “1 out of 1,000” to “1 out of 10,000” uses. “Common” is the uniform term used for events that happen in between “1 out of 10” to “1 out of 100” uses.<sup>66</sup> Given that “about 1 out of 100 women” using Mifeprex/misoprostol require surgery, serious complications are common, not rare.<sup>67</sup>

Also, as discussed in Section I.C above, Mifeprex abortions carry greater risks than surgical abortions.<sup>68</sup> A study of over 42,000 women in Finland who had abortions from 2000 to 2006 found that “overall, medical abortion had roughly four times the rate of adverse events than surgical abortion, and hemorrhaging was experienced by 16 percent of medical abortion patients compared with 2 percent of surgical abortion patients.”<sup>69</sup>

A combined retrospective and longitudinal follow-up study of complications related to induced abortion in Sweden published in 2018 determined that the share of complications related to drug-induced abortions at less than 12 weeks *increased* significantly during 2008-2015 without an evident cause. The increase was from 4.2% in 2008 to 8.2% in 2015, with incomplete abortion as the most common complication related to drug-induced abortions at less than 12 weeks.<sup>70</sup>

Abortion advocates are also attacking the REMS by advocating for mifepristone use in spontaneous miscarriage management. In a small recent study, researchers compared the efficacy and safety of using mifepristone with misoprostol for the management of early miscarriages to using misoprostol alone.<sup>71</sup> Notably, 6-10% of study participants had a gestational age of “4-5 weeks gestation.”<sup>72</sup> It is not clear from the authors how participants of that gestational age could meet the published guidelines for diagnosis of non-viable pregnancy recently published by the Society of Radiologists in Ultrasound multispecialty consensus panel.<sup>73</sup> The panel requires the crown-rump length cutoff to 7 mm for embryos without a heartbeat and the mean sac diameter cutoff to 25 mm for

---

<sup>66</sup> CIOMS training manual on medicine safety, [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/trainingcourses/definitions.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf).

<sup>67</sup> See Mifeprex Medication Guide; CIOMS training manual on medicine safety, *supra*.

<sup>68</sup> See Harrison Aff. ¶ 115; ACOG Practice Bulletin 143, p. 3 & Box 1.

<sup>69</sup> GAO-18-292, p. 25, *discussing* Niinimäki M, et al., *Immediate Complications after Medical Compared with Surgical Termination of Pregnancy*, *Obstetrics & Gynecology*, vol. 114, no. 4 (October 2009): 795-804.

<sup>70</sup> Carlsson I, Breeding K, and Larsson PG, *Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study*, *BMC Women's Health* (2018) 18:158.

<sup>71</sup> Schreiber CA, et al., *Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss*, *N Engl J Med* 2018; 378:2161-70.

<sup>72</sup> *Id.* Table 1.

<sup>73</sup> Doubilet PM, Benson CB, Bourne T, et al., *Diagnostic criteria for nonviable pregnancy early in the first trimester*, *N Engl J Med* 2013; 369:1443-1451.

“empty” sacs, in order to minimize interventions that “interrupt a pregnancy that otherwise would have had a normal outcome.”<sup>74</sup>

The authors admit that the study “was not powered to show differences between groups in the proportions of serious adverse events,”<sup>75</sup> an important consideration prior to recommending a change in spontaneous abortion management protocols. Yet, the authors incorrectly stated “such events were rare.”<sup>76</sup> Table 3 gives a total number of serious adverse events as 3.4% for the mifepristone pretreatment group, and 2.0% for the misoprostol alone group.<sup>77</sup> Under the CIOMS criteria for reporting complications from drugs, discussed above, the rate of 2%-3.4% of adverse events in each study arm demonstrates clearly that adverse events are common, not rare, in both misoprostol alone and mifepristone + misoprostol miscarriage management.

Further, the Mifeprex + misoprostol arm raises a concern about the need for further study of adverse events, especially hemorrhage. Mifepristone is known to inhibit endometrial hemostasis (*i.e.*, arrest of bleeding),<sup>78</sup> as demonstrated by many reports of hemorrhage with transfusions reported to the FDA after use of mifepristone and misoprostol for elective abortions.<sup>79</sup>

Of additional concern is the vaginal route of administration of misoprostol. After reports of overwhelming sepsis following vaginal administration of misoprostol, Planned Parenthood changed the route of administration of misoprostol from vaginal to buccal,<sup>80</sup> with subsequent decrease in reported infections. Animal studies have demonstrated that both mifepristone<sup>81</sup> and misoprostol<sup>82</sup> can profoundly suppress innate immunity and the ability to fight infections.

<sup>74</sup> Hu M, Poder L, Filly R, *Impact of New Society of Radiologists in Ultrasound Early First-Trimester Diagnostic Criteria for Nonviable Pregnancy*, J Ultrasound Med 2014; 33:1585–1588.

<sup>75</sup> Schreiber, *supra* p. 2168.

<sup>76</sup> *Id.*

<sup>77</sup> *Id.* p. 2169.

<sup>78</sup> Miech RP, *Pathopharmacology of excessive hemorrhage in mifepristone abortions*, Ann Pharmacother 2007 Dec; 41(12):2002-7.

<sup>79</sup> Gary MM, Harrison DJ. “Analysis of severe adverse events related to the use of mifepristone as an abortifacient.” Ann Pharmacother. 2006 Feb;40(2):191-7; Food and Drug Administration “Mifepristone U.S. Postmarketing Adverse Events Summary” 2011,

[https://www.minnpost.com/sites/default/files/attachments/Mifeprex\\_April2011\\_AEs.pdf](https://www.minnpost.com/sites/default/files/attachments/Mifeprex_April2011_AEs.pdf).

<sup>80</sup> Fjerstad M, Trussell J, Sivin I, Lichtenberg ES, Cullins V, *Rates of Serious Infection after Changes in Regimens for Medical Abortion*, N Engl J Med 2009; 361:145-51.

<sup>81</sup> Sternberg EM, Hill JM, Chrousos GP, Kamilaris T, Listwak SJ, Gold PW, Wilder RL, *Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats*, Proc Natl Acad Sci U S A. 1989 Apr;86(7):2374-8; Miech RP, *Pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii*, Ann Pharmacother. 2005 Sep;39(9):1483-8. Epub 2005 Jul 26.

<sup>82</sup> Aronoff DM et al., *Misoprostol impairs female reproductive tract innate immunity against clostridium sordellii*, 180 J. Immunol. 8222-8230 (2008).

Despite the clear methodological errors, including a failure to accurately diagnose fetal death according to accepted criteria as well as lack of adherence to the stated inclusion criteria, and despite the absence of power to evaluate safety, abortion advocates are calling for the routine use of mifepristone to manage spontaneous miscarriages.<sup>83</sup> Any change in spontaneous miscarriage management with mifepristone should require an FDA New Drug Application (NDA) with two randomized controlled trials (RCTs) comparing the arms of mifepristone and misoprostol, misoprostol alone, surgical management, and expectant management. Without blinded RCTs to evaluate not only efficacy but also safety, it is premature to remove the REMS for Mifeprex to facilitate mifepristone access for spontaneous miscarriage management.

Despite the presence of serious risks and contraindications to the Mifeprex regimen, Gynuity, the University of California, San Francisco (UCSF), and other abortion advocates want the FDA to eliminate the remaining safeguards that were enacted to ensure the safety and efficacy of Mifeprex. They are pursuing their goals through publication, advocacy, litigation,<sup>84</sup> and/or controversial research enabled by FDA.<sup>85</sup>

Further, as Section II.B below explains, lifting the REMS is only the starting point for abortion advocates.

**B. Continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.**

1. Mifeprex should be dispensed only in clinics, medical offices, and hospitals.

The Mifeprex REMS requires that Mifeprex “be dispensed to patients only in clinics, medical offices and hospitals, by or under the supervision of a certified prescriber.” That prescriber must be capable of assessing the duration of a pregnancy accurately, diagnosing ectopic pregnancies, and providing or referring for surgical intervention in cases of incomplete abortion or hemorrhaging.<sup>86</sup>

Abortion advocates, however, want the FDA to permit healthcare providers to prescribe Mifeprex to pregnant patients over the Internet or phone, with the drug available at pharmacies or through the mail, and through advance provision (*i.e.*, before a patient is pregnant). Eliminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls. Healthcare providers

---

<sup>83</sup> Molly Walker, *Mifepristone: Better for Managing Early Miscarriage*, Medpage Today, (June 6, 2018), <https://www.medpagetoday.com/obgyn/pregnancy/73336>.

<sup>84</sup> *Chelius v. Azar*. CIV. NO. 1:17-cv-00493-DKW-KSC (Dist. Ct. HI 2018).

<sup>85</sup> See Section II.B, below.

<sup>86</sup> Mifeprex Risk Evaluation and Mitigation Strategy (REMS), [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf).



prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs.<sup>87</sup> Further, as discussed above, Rh-negative patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without direct patient contact, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies.<sup>88</sup> [See Section I.B.2, *supra*.]

Telemedicine abortion further distances women from the practitioners responsible for caring for them, and approval by FDA would further absolve abortion providers of responsibility for the well-being of their patients. Promoting telemedicine abortion to women and adolescent girls in rural areas with limited access to healthcare is extremely dangerous—they will have little recourse if they face known and predictable emergency complications such as severe hemorrhage.<sup>89</sup>

Nonetheless, Gynuity Health Projects and researchers from UCSF obtained approval from FDA through Investigational New Drug Applications (INDs) to conduct studies that *do not* comply with the Mifeprex REMS. They will use the results of these studies to press for the elimination of the Mifeprex REMS.

#### a. The “TelAbortion” Direct-to-Consumer Mifeprex Study

Gynuity Health Projects is the sponsor of the study “Feasibility of Medical Abortion by Direct-to-Consumer Telemedicine.”<sup>90</sup> Gynuity filed an IND with the FDA.<sup>91</sup> The status is listed as “recruiting,” with age eligibility that includes 11-year-old children and an estimated enrollment of 1,000 participants at five locations.<sup>92</sup> The start date is listed as March 22, 2016, and the estimated completion date was extended from June 2018 to June 2019.

The study’s brief summary states: “This pilot study is designed to obtain preliminary data on the safety, acceptability, and feasibility of direct-to-consumer telemedicine

<sup>87</sup> Harrison & Norton Testimony, p. 2.

<sup>88</sup> ACOG Practice Bulletin 181: *Prevention of Rh D Alloimmunization* (Aug. 2017); and SOGC Clinical Practice Guidelines: *Prevention of Rh Alloimmunization* (No. 133, Sept. 2003).

<sup>89</sup> Harrison & Norton Testimony, p. 9.

<sup>90</sup> (NCT02513043), <https://www.clinicaltrials.gov/ct2/show/NCT02513043?term=NCT02513043&rank=1>.

<sup>91</sup> Raymond EG, Chong E, & Hyland P, *Increasing Access to Abortion with Telemedicine*, JAMA Internal Medicine Vol. 176, N. 5 (May 2016).

<sup>92</sup> Hawaii – University of Hawaii Women’s Options Center; Maine – Maine Family Planning; New York – Choices Women’s Medical Center (active, but not recruiting according to ClinicalTrials.gov, and not listed on TelAbortion.org); Oregon and Washington – Planned Parenthood Columbia Willamette; Oregon Health and Sciences University Women’s Health Research Unit. Washington State patients may also participate because an Oregon abortion provider is also licensed in Washington State. Claire Lampen, [Webcam Abortion Services Offer Crucial Access—So What’s Stopping them?](#) Gizmodo (Apr. 17, 2018).

abortion.”<sup>93</sup> The study’s website states that “[a] TelAbortion involves all the same steps and procedures as a regular medical abortion, but you do them without going into an abortion clinic.”<sup>94</sup>

Women who participate in the study have a video “evaluation” with the study abortion provider over the Internet, during which they can ask questions, provide medical history, and learn about the pre-abortion tests that they need. They also electronically sign consent forms for the study. Afterwards, they are required to obtain the tests and direct the reports to be sent to the study provider.

Once a patient is determined eligible, the study provider will send her a package containing Mifeprex and misoprostol, with instructions that she must follow on her own. She is also instructed to have additional tests to verify that the abortion is complete, and later have another consultation with the study provider to review the results.<sup>95</sup>

Obviously, a woman may *not* take the abortion drugs in the manner prescribed, nor obtain the follow-up care that is recommended. With a doctor-patient relationship limited to online chats, she has virtually no accountability or support as she navigates a complicated procedure. The responsibility of the provider of the drugs to follow up with the patient is obviated as well.

#### **b. The Mifeprex through Pharmacy Dispensing Study**

The University of California, San Francisco (UCSF) is the sponsor of the “Alternative Provision of Medication Abortion via Pharmacy Dispensing” study.<sup>96</sup> Daniel Grossman, M.D., with UCSF is listed as the study’s “responsible party.”<sup>97</sup> Like Gynuity, UCSF filed an IND with the FDA to obtain authorization for this study.<sup>98</sup> The status is listed as “recruiting,” with July 2019 as the estimated completion date. The sponsors plan to recruit 300 patients at four study clinic sites and survey 50 pharmacists at associated study pharmacy sites.<sup>99</sup>

---

<sup>93</sup> NCT02513043, <https://www.clinicaltrials.gov/ct2/show/NCT02513043?term=NCT02513043&rank=1>.

<sup>94</sup> TelAbortion: The Telemedicine Abortion Study: FAQs, <http://telabortion.org/faq/>.

<sup>95</sup> *Id.*

<sup>96</sup> NCT03320057, <https://www.clinicaltrials.gov/ct2/show/NCT03320057?term=NCT03320057&rank=1>; Daniel Grossman, MD, Research Protocol: *Alternative Provision of Medication Abortion via Pharmacy Dispensing*, Version #:1.3 (JUL. 17, 2018) p. 5.

<sup>97</sup> *Id.*

<sup>98</sup> In a May 2018 phone conversation with a contact for the UCSF study, she stated that the study was approved through an IND application with FDA.

<sup>99</sup> Grossman, pp. 5-7; 16-17.

The stated aim of the study is to “investigate the feasibility, acceptability, and effectiveness of pharmacy dispensing of Mifeprex; safety data will also be collected. . . . *The results of this study eventually could lead to changes in the Mifeprex REMS. . . .*”<sup>100</sup>

The sponsors intend to measure “pharmacist satisfaction with dispensing Mifeprex and the proportion of pharmacists who refuse to dispense the medication to patients.” They secondarily intend to assess patient satisfaction, describe clinical outcomes, including effectiveness and adverse events, and compare pharmacists’ knowledge about medication abortion before and after.<sup>101</sup>

Patients enroll at one of the study clinic sites on Day 1, where they choose medication abortion, have an ultrasound if one has not been done, and obtain pre-abortion counseling. They then are prescribed Mifeprex, misoprostol, and anything else necessary to be filled at the associated study pharmacy site.<sup>102</sup> Some patients have serum hCG measured on the day of Mifeprex administration and again around eight days later “to assess for completion of the abortion.”<sup>103</sup> The “follow-up” for patients “may include a follow-up visit or a phone call from clinic staff approximately 7-14 days after the initial visit.”<sup>104</sup> However, as discussed extensively above, a clinician needs to perform an exam to rule out retained tissue—even if the patient has a negative serum hCG. A phone call that “may” be placed, or fail to connect, is not enough.

Notably, “[a]ll except one of [the participating] pharmacies is [sic] located within the same building as the clinic....”<sup>105</sup> While UCSF is using a community pharmacy not affiliated with the University, the other three study clinic sites are using affiliated pharmacies.<sup>106</sup>

---

<sup>100</sup> Grossman, p.14 (emphasis added). The sponsors dubiously assert that “pharmacy dispensing could [] help increase the number of clinicians willing and able to provide medication abortion by enabling them to avoid the associated costs and logistical challenges of stocking and dispensing the medication at their facilities.” They reference a survey of Fellows of the American College of Obstetricians and Gynecologists that sought to determine if doctors not presently practicing abortion would prescribe Mifeprex if their patients could obtain the drug at a pharmacy. Fifty-four percent responded to the survey. Seventy-seven percent of respondents *do not* perform abortions and nine percent perform surgical abortions only—of those, 19% said they would prescribe Mifeprex if it could be obtained at a pharmacy, and an additional 18% said they were unsure. Based on this, the sponsors claim “the proportion of obstetrician-gynecologists providing [Mifeprex] would at least double (from 14% to 29%) “if the dispensing restriction in the REMS were removed and physicians could write a prescription for Mifeprex that could be dispensed at a pharmacy.” The fact that 46 percent of the fellows surveyed did not take the time to respond, however, places this conclusion in doubt. *See* Grossman, pp. 12-14.

<sup>101</sup> Grossman, pp. 15-16.

<sup>102</sup> Grossman, p. 23.

<sup>103</sup> Grossman, p. 23.

<sup>104</sup> Grossman, p. 24.

<sup>105</sup> Grossman, p. 20.

<sup>106</sup> Grossman, pp 16-17.



While the rationale for the study states that pharmacy dispensing of Mifeprex could “help facilitate provision of medication abortion through telemedicine,”<sup>107</sup> the sponsors emphasize that the only difference between this study and FDA protocol “is that the patient would obtain the mifepristone directly from the pharmacist, rather than in a clinic facility.”<sup>108</sup> In fact, the schedules for the participating pharmacists are “mapped” to “ensure that trained pharmacists are available to dispense to study participants during business hours.”<sup>109</sup>

The following demonstrates the extensive assistance that the sponsors offer patients in obtaining the drugs from the participating pharmacies:

[The patient] will be told that only a limited number of pharmacies are able to dispense Mifeprex and given information about how to get to the participating pharmacy (as well as the hours during which a participating pharmacist will be working, if needed). If there are any gaps in staffing at the pharmacy, the patient will be notified of the timing of those gaps in coverage before leaving the clinic via the pharmacy directions/handout. If this will be an issue for the patient, a solution will be found at the clinic before the patient leaves or she will not be enrolled in the study. Patients will be told that if they have any problems accessing the medications at the clinic, they should come back to the clinic [where they can obtain Mifeprex].<sup>110</sup>

While this assistance may ensure that the study does not deviate dramatically from FDA protocol, the study *certainly* does not model the experience a patient would have outside of this controlled environment—particularly a patient who obtains Mifeprex through telemedicine and has no physical contact with her prescriber.

The physical proximity of the study pharmacy sites to the study clinic sites, the probable professional associations between participating doctors and pharmacists, and the extensive assistance offered by the clinics to ensure that patients access abortion-inducing drugs at participating pharmacies, raise questions as to whether the study is fundamentally biased and will inaccurately forecast widespread behavior and experiences if the REMS is removed. Therefore, any results of the study cannot provide a justification for permitting pharmacy distribution of Mifeprex, much less abortion through telemedicine.

---

<sup>107</sup> Grossman, p. 6.

<sup>108</sup> Grossman, p. 6.

<sup>109</sup> Grossman, p. 18.

<sup>110</sup> Grossman, pp. 19-20.

Further, as discussed below, eliminating the REMS to enable pharmacy dispensing of Mifeprex is only the beginning of a long-term strategy to achieve over-the-counter status for Mifeprex, further diminishing patient care and abortion provider accountability.

**c. Beyond the Current Studies**

A recent article by Dr. Grossman and colleagues reveals that they want Mifeprex access extended even beyond the parameters contained in their Pharmacy Dispensing study. They used an online survey to gauge women’s “personal interest in and general support for three alternative methods for accessing abortion pills: (1) in advance from a doctor for future use, (2) over-the-counter (OTC) from a drugstore and (3) online without a prescription.”<sup>111</sup>

None of the options in the survey require a healthcare provider to provide patient care comparable to even the *inadequate* care provided in the two studies discussed above. Only the first option requires a prescription from a doctor; however, the doctor would not know in advance when his patient actually becomes pregnant and chooses to use the drugs. The survey disingenuously stated that “[m]edication abortion, or the abortion pill, is a safe and effective way to terminate a pregnancy up to 10 weeks,” without informing participants of a single risk associated with the regimen.<sup>112</sup>

Further, in a November, 21, 2018 op-ed, Dr. Grossman advocated for providing abortion pills before women are pregnant. He stated:

The idea is simple: Give women abortion pills *before* they need them – “advance provision,” as it’s known – so that they can take them as soon as they discover a pregnancy. Women could get the pills from their gynecologist at the time of their annual exam, say, or the pills could be made available online.<sup>113</sup>

Incredibly, Dr. Grossman stated that he has “few medical concerns about handing out abortion pills in advance.”<sup>114</sup> He asserts that evidence from advance provision research “could strengthen the case for making [abortion-inducing drugs] available without a prescription.”<sup>115</sup>

---

<sup>111</sup> Biggs MA, et al, *Support for and interest in alternative models of medication abortion provision among a national probability sample of U.S. women*, *Contraception* (2018), <https://doi.org/10.1016/j.contraception.2018.10.007>.

<sup>112</sup> *See id.*

<sup>113</sup> Daniel Grossman, *American women should have access to abortion pills before they need them*, *Los Angeles Times* (Nov. 21, 2018).

<sup>114</sup> *Id.*

<sup>115</sup> *Id.*

In addition to his failure to address all of the dangers posed by abortion-inducing drugs, Dr. Grossman does not acknowledge the risk that women will share their abortion-inducing pills with other women. While an abortion provider may screen his patient for contraindications to Mifeprex, nothing will stop his patient from giving her stored Mifeprex to a friend who is unaware that she is Rh negative, for instance, which poses health risks for future pregnancies (See section I.B.2, *supra*).

In fact, Dr. Grossman's research program has listed a study titled "Alternative Provision of Medication Abortion Via Advance Provision" on ClinicalTrials.gov, with May 2019 listed as the estimated study start date.<sup>116</sup> In the study, patients who are "at risk of unintended pregnancy and with a desire to avoid pregnancy will be assessed by a clinician and provided counseling on pregnancy recognition and testing, as well as how to administer [drug-induced abortion] at home." They will then receive Mifeprex and misoprostol while *not* pregnant. If/when the patient becomes pregnant and wants to take the drugs, she is instructed to contact a study clinician for an "over-the-phone assessment of eligibility" for drug-induced abortion, "including evaluation of contraindications and gestational age" before taking the drugs, and "then attend a follow-up visit with the clinician."<sup>117</sup> However, it is impossible for the study sponsors to truly assess the patient for contraindications, verify gestational age, prevent patients from sharing the drugs with others, or ensure that patients attend a follow-up visit.

In a 2018 Policy Review, the Guttmacher Institute also advocated for lifting the Mifeprex REMS. However, the article did not stop there. The author argues:

[w]hile lifting the REMS on mifepristone would open new possibilities for medication abortion access, stopping there would fall short of realizing the full potential of this method, particularly when it comes to self-managed abortion care. In a self-management model, anyone who needs to terminate a pregnancy would be able to legally access mifepristone and misoprostol without a requirement to see a health care provider or pharmacist first. . . . To fully integrate self-managed medication abortion with existing abortion practices in the United States, misoprostol and mifepristone must first become available without a prescription.<sup>118</sup>

These recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex. In spite of the serious risks and contraindications to the Mifeprex regimen, abortion advocates will not rest until Mifeprex is available to all, without a prescription

---

<sup>116</sup> NCT03829696, <https://clinicaltrials.gov/ct2/show/NCT03829696?term=NCT03829696&rank=1>.

<sup>117</sup> *Id.*

<sup>118</sup> Donovan MK, *Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care*, Guttmacher Policy Review, vol. 21 (2018).



or mandatory medical management of any kind. The FDA's vigilance in protecting women from such negligence is critically important.

## 2. Mifeprex Prescribers Should be Certified.

The 2016 regimen requires Mifeprex prescribers to be certified as qualified. This is simply common sense—only healthcare providers qualified to prescribe an abortion-inducing drug should do so. The prescriber form attests that the healthcare provider must be able to assess pregnancy duration, diagnose ectopic pregnancy, and provide or refer for surgical intervention if necessary.

Given that drug-induced abortion is contraindicated beyond 10 weeks' gestation and when the pregnancy is not in the uterus, and that *at least* 1 out of 100 women using Mifeprex need surgery,<sup>119</sup> these qualifications are entirely logical. Yet, abortion advocates, ignoring the best interests of their patients, claim such restrictions are onerous.<sup>120</sup>

## CONCLUSION

The Mifeprex REMS with ETASU remains critical for patient safety. Mifeprex carries risks of life-threatening hemorrhage, infection, continued pregnancy, retained tissue, need for emergency surgery, and death. The 2000 regimen provided significantly more protections for patients than the 2016 regimen. FDA should restore and strengthen elements of the Mifeprex regimen and provider requirements, including: limiting Mifeprex use to 49 days' gestation; requiring that Mifeprex be administered only by or under the supervision of a physically present physician; requiring three office visits by a patient who has been prescribed Mifeprex; clarifying that Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care; expanding mandatory adverse event reporting; and requiring additional studies of Mifeprex use in at-risk populations.

At the very least, FDA should not further erode patient protections. The agency should retain the Mifeprex REMS, and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

---

<sup>119</sup> Mifeprex Risk Evaluation and Mitigation Strategy (REMS), [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf).

<sup>120</sup> Mifeprex REMS Study Group, *Sixteen Years of Overregulation: Time to Unburden Mifeprex*, N Engl. J. Med. 376:8 (Feb. 23, 2017).

**C. Environmental Impact**

This petition is categorically excluded under 21 C.F.R. § 25.30.

**D. Economic Impact**

Available upon Commissioner's request, pursuant to 21 C.F.R. §10.30(3).

**E. Certification**

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners, which are unfavorable to the petition.

**Signature:** /s/ Donna J. Harrison M.D., Executive Director

**Name of petitioner:** American Association of Pro-Life Obstetricians and Gynecologists

**Mailing address:** PO Box 395, Eau Claire, MI 49111-0395

**Telephone number:** (202) 230-0997

**Signature:** /s/ Quentin L. Van Meter, M.D., FCP, President

**Name of petitioner:** American College of Pediatricians

**Mailing address:** PO Box 357190, Gainesville, FL 32635-7190

**Telephone number:** (352) 376-1877

# Exhibit 36

2019 FDA Abbreviated New Drug Application (ANDA)  
Approval Letter to GenBioPro, Inc. (Apr. 11, 2019)





ANDA 091178

**ANDA APPROVAL**

(b) (6), (b) (4)  
GenBioPro, Inc.  
(b) (6), (b) (4)  
Attention: (b) (6), (b) (4)

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 3, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mifepristone Tablets, 200 mg.

Reference is also made to the complete response letter issued by this office on February 23, 2018, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The (b) (6) has determined your Mifepristone Tablets, 200 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Mifeprex Tablets, 200 mg, of Danco Laboratories, LLC.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our letter dated June 15, 2011. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your REMS, known as the Mifepristone REMS Program, submitted on May 30, 2017; is approved, and will be posted on the FDA REMS website: <http://www.fda.gov/rem>

The REMS consists of ETASU and an implementation system.

U.S. Food & Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

Your REMS must be fully operational before you introduce Mifepristone Tablets, 200 mg, into interstate commerce.

The Mifepristone REMS uses a single, shared system for the ETASU. This single, shared system REMS Program currently includes the products listed on the FDA REMS website, available at <http://www.fda.gov/remes>. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

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

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

**ANDA 091178 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR ANDA 091178/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR ANDA 091178/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR ANDA 091178/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

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

## **REMS REVISION FOR ANDA 091178**

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

### **SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

In addition to submitting the proposed REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email [REMSWebsite@fda.hhs.gov](mailto:REMSWebsite@fda.hhs.gov)

### **REPORTING REQUIREMENTS**

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506l of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506l(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

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



You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **ANNUAL FACILITY FEES**

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions<sup>1</sup> with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1<sup>st</sup> of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

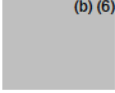
*{See appended electronic signature page}*



Center for Drug Evaluation and Research

---

<sup>1</sup> Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Digitally signed by (b) (6)

Date: 4/11/2019 02:22:21PM

GUID: 54078879000a1b9e15dd31ed6f0343ca



# Exhibit 37

2019 FDA Supplemental Approval Letter to Danco  
Laboratories, LLC (Apr. 11, 2019)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 020687/S-022

**SUPPLEMENT APPROVAL**

Danco Laboratories, LLC  
(b) (4), (b) (6)

P.O. Box 4816  
New York, NY 10185

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

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

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

**APPROVAL & LABELING**

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

**CONTENT OF LABELING**

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

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

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

The SPL will be accessible from publicly available labeling repositories.

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

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

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

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

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

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

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

#### **REMS Assessment Plan**

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

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



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

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

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

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

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

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

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

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

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

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

**NDA 020687 REMS ASSESSMENT**

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

*Or*

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

*Or*

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

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

of the submission:

#### **REMS REVISIONS FOR NDA 020687**

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

#### **SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

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

For more information on submitting REMS in SPL format, please email [REMS\\_Website@fda.hhs.gov](mailto:REMS_Website@fda.hhs.gov).

#### **REQUIRED PEDIATRIC ASSESSMENTS**

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

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

#### **REPORTING REQUIREMENTS**

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

If you have any questions, call

(b) (6)

Sincerely,

*{See appended electronic signature page}*

(b) (6)

Center for Drug Evaluation and Research



ENCLOSURES:

Content of Labeling  
Prescribing Information  
Medication Guide  
REMS

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

-----  
/s/  
-----

(b) (6)

04/11/2019 02:13:59 PM

# Exhibit 39

2021 FDA Letter to Am. Coll. of Obstetricians &  
Gynecologists and Soc'y for Maternal-Fetal Med. about  
Mifepristone REMS (Apr. 12, 2021)





April 12, 2021

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

Skye Perryman, General Counsel  
[sperryman@acog.org](mailto:sperryman@acog.org)

William Grobman, MD, MBA  
President  
Society for Maternal-Fetal Medicine  
[w-grobman@northwestern.edu](mailto:w-grobman@northwestern.edu)

Dear Drs. Phipps and Grobman,

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

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

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

---

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

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

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

In summary, provided the other requirements of the Mifepristone REMS Program are met, and given that the in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare personnel because it may involve a clinic visit solely for this purpose, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form. Further, to the extent all of the other requirements of the Mifepristone REMS Program are met, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

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

Sincerely yours,



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

---

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

# Exhibit 41

2021 Updated REMS Mifepristone Tablets,  
200 mg (May 14, 2021)



Initial Shared System REMS approval: 04/2019  
Most Recent Modification: 05/2021

Mifepristone Tablets, 200 mg

Progestin Antagonist

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

**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 in certain healthcare settings by or under the supervision of a certified prescriber.
- 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 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-v below).
  - b. As a condition of certification, healthcare providers must follow the guidelines for use of mifepristone described below:
    - i. 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.

- 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 mifepristone in each patient's record.
  - vi. Report any deaths to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and the serial number from each package of mifepristone.
- 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. Provide the Prescribing Information and their *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 for Danco Laboratories, LLC*
  - *Prescriber Agreement Form for GenBioPro, Inc.*
  - *Patient Agreement Form*
2. 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.
- a. Mifepristone Sponsors must:
- i. Ensure that their mifepristone 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 their mifepristone is not distributed to or dispensed through retail pharmacies or other settings not described above.
3. Mifepristone 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 the patient 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 mifepristone.

## **B. Implementation System**

1. Mifepristone Sponsors must ensure that their mifepristone 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 their mifepristone 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 a Prescriber Agreement Form.
    - b. Notify healthcare providers when they have been certified by the Mifepristone REMS Program.
    - c. Ship mifepristone only to clinics, medical offices, and hospitals identified by certified prescribers in their signed *Prescriber Agreement Form*.
    - d. Not ship mifepristone to prescribers who become de-certified from the Mifepristone REMS Program.
    - e. 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, 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, FDA or a third party acting on behalf of Mifepristone Sponsors or FDA 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 REMS Program.
  3. Mifepristone Sponsors must audit their 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 Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.
  4. 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.
  5. 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 applicant. This requirement does not affect the applicants 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 initial approval of the REMS (04/11/2019) 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 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.



# Exhibit 42

2021 FDA Center for Drug Evaluation and Research  
Director Patrizia Cavazzoni Letter to Dr. Graham  
Chelius (Dec. 16, 2021)



Center for Drug Evaluation and Research

Food and Drug Administration

---

December 16, 2021

Graham Chelius, M.D.  
The Society of Family Planning  
The California Academy of Family Physicians

Dear Dr. Chelius:

This letter is to inform you that FDA has completed its review of the Mifepristone Risk Evaluation and Mitigation System (REMS) Program.<sup>1</sup> The agency has determined that the Mifepristone REMS Program continues to be necessary to ensure that the benefits of the drug outweigh the risks. However, we have determined that it must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. See 21 USC 355-1(g)(4)(B). The modifications to the REMS will consist of: (1) removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”); and (2) adding a requirement that pharmacies that dispense the drug be specially certified.

A REMS Modification Notification letter has been sent to both Applicants subject to the Mifepristone REMS Program. The letter describes the modifications and directs the Applicants to submit prior approval supplements within 120 days. We have also answered a related citizen petition from the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians. That response will be posted in the public docket (Docket No. FDA-2019-P-1534; available at [www.regulations.gov](http://www.regulations.gov)).

Sincerely,

Patrizia Cavazzoni, M.D.  
Director  
Center for Drug Evaluation and Research

<sup>1</sup> We also note your letter of September 29, 2021 to us on this subject.

# Exhibit 43

2021 FDA Letter to Am. Ass'n of Pro-Life Obstetricians & Gynecologists and Am. Coll. of Pediatricians denying in part and granting in part 2019 Citizen Petition, Docket No. FDA-2019-P-1534 (Dec. 16, 2021) (2019 Petition Denial)





Donna J. Harrison, M.D.  
Executive Director  
American Association of Pro-Life Obstetricians and Gynecologists  
P.O. Box 395  
Eau Claire, MI 49111-0395

Quentin L. Van Meter, M.D., FCP  
President  
American College of Pediatricians  
P.O. Box 357190  
Gainesville, FL 32635-7190

December 16, 2021

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

Dear Drs. Harrison and Van Meter:

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

Specifically, in your Petition you request that the Agency:

- (1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:
  - Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.
  - Dosage and Administration:
    - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.
    - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

U.S. Food & Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

Docket No. FDA-2019-P-1534

- Contraindications - Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.
- Adverse Event Reporting - Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.
- Additional studies - The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

(2) Retain the Mifeprex REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is granted in part and denied in part.

## **I. BACKGROUND**

### **A. Mifeprex**

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H), "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.<sup>1</sup>

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.<sup>2</sup> Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use included: (1) prescriber certification (ETASU A); (2) that Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber

<sup>1</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/appltr/2000/20687appltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/appltr/2000/20687appltr.pdf).

<sup>2</sup> 73 FR 16313 (Mar. 27, 2008).

Docket No. FDA-2019-P-1534

(ETASU C); and (3) that Mifeprex is dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the applicant Danco Laboratories, LLC (S-020 efficacy supplement). The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective, as well as the process for follow-up after administration of the drug.

Specifically, the following changes, among others, were made as part of the 2016 approval:<sup>3</sup>

- Revised the dosing regimen to consist of 200 mg of Mifeprex taken by mouth, followed in 24-48 hours by 800 mcg of misoprostol taken buccally (in the cheek pouch). This differs from the originally approved dosing regimen of 600 mg of oral Mifeprex followed 48 hours later by 400 mcg of oral misoprostol.
- Revised the indication for use of Mifeprex, in a regimen with misoprostol, to extend the maximum gestational age for the medical termination of intrauterine pregnancy from 49 days to 70 days.
- Reduced the number of office visits by the patient under the approved regimen from three to one.
- Replaced the term “physician” with the term “healthcare provider.”

In addition, after reviewing the data and information submitted by the applicant in the S-020 efficacy supplement, and after taking into consideration the safety data that had become available since the initial approval of Mifeprex in 2000, we determined the Mifeprex REMS continued to be necessary to ensure the benefits of the product outweigh the risks. However, we approved modifications to the Mifeprex REMS that reflected the changes approved in the efficacy supplement. These changes to the REMS included, among others:<sup>4</sup>

- Updating the Prescriber Agreement Form to reflect the revised indication and dosing regimen.
- Removing the Medication Guide as a REMS element (but retaining the Medication Guide as labeling).

<sup>3</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2016/020687Orig1s020ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf) and [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf).

<sup>4</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/020687Orig1s020RemsR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf).



Docket No. FDA-2019-P-1534

- Removing the requirement that certified prescribers report certain enumerated adverse events to the applicant (specifically, any hospitalization, transfusion or other serious adverse events), but retaining the requirement that certified prescribers report all deaths to the sponsor.

Under the March 2016 approval, the Mifeprex REMS also continued to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.<sup>5</sup>

### **B. Generic Version of Mifeprex**

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). This action took place after this Petition was submitted to the Agency. As required by 21 CFR 314.94(a)(8), GenBioPro's approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex. Accordingly, although we refer to the Mifeprex labeling in several sections of this response, our discussions in this response apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.<sup>6</sup>

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. -1(i)). At the time we approved GenBioPro's generic version of Mifeprex, that ANDA product was required to use a single, shared system for the ETASU with the brand drug product, Mifeprex, unless the requirement was waived by FDA (21 U.S.C. 355-1(i)). FDA did not waive this requirement. Accordingly, at the same time that FDA approved GenBioPro's generic version of Mifeprex in 2019, FDA approved a supplemental new drug application (sNDA) for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In establishing the single, shared system REMS in 2019, no substantive changes were made to the ETASU in the March 2016 Mifeprex REMS. References to the REMS in this response refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

### **C. In-Person Dispensing Requirement During the COVID-19 PHE**

---

<sup>5</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2016/020687Orig1s020ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/020687Orig1s020ltr.pdf).

<sup>6</sup> We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone - as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

Docket No. FDA-2019-P-1534

FDA has recognized that during the COVID-19<sup>7</sup> public health emergency (PHE),<sup>8</sup> certain REMS requirements for various products may be difficult to comply with because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. The Agency has also received queries concerning products with REMS that have ETASUs, including REMS with ETASUs that restrict distribution, and the impact of such ETASUs on patient access when patients self-isolate or are subject to quarantine.

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 PHE regarding the requirement in the Mifepristone REMS Program that mifepristone used for medical termination of intrauterine pregnancy through 70 days gestation be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the “in-person dispensing requirement”).

Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020 to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.<sup>9</sup>

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

FDA’s intent to exercise enforcement discretion with respect to these requirements during the COVID-19 PHE was the result of a thorough scientific review by experts within FDA’s Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports.

#### **D. Minor Modification**

---

<sup>7</sup> The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19).

<sup>8</sup> Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

<sup>9</sup> *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).

Docket No. FDA-2019-P-1534

In response to a request submitted by the applicants, FDA approved a minor modification to the Mifepristone REMS Program on May 14, 2021. This minor modification revised the Patient Agreement Form to use gender neutral language. Specifically, the pronouns “she” and “her” in the Patient Agreement Form were replaced with “the patient.” The minor modification also included revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form. These changes did not affect the substance of the Patient Agreement Form, the REMS document, or the Mifepristone REMS Program.

#### **E. Review of the Mifepristone REMS Program**

In 2021, FDA also undertook a full review of the Mifepristone REMS Program.<sup>10</sup> In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA (together, the Applicants). As discussed in more detail below, based on our review of this information, FDA has determined that certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation; and therefore, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risk. Specifically, we find that the healthcare provider certification and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions continue to be necessary components of the REMS to ensure the benefits of mifepristone outweigh the risks for this indication.

We also find that the in-person dispensing requirement is no longer necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation. We have concluded that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added.<sup>11</sup> Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Accordingly, today we are sending a REMS Modification Notification letter to both Applicants in the Mifepristone REMS Program. As stated in that letter, FDA has concluded that a modification is necessary and must include the following changes:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

---

<sup>10</sup> We note that the Agency is in litigation regarding the Mifepristone REMS Program and committed to conducting a full review of the Mifepristone REMS Program, including reviewing any relevant data and evidence submitted to the Agency by the Plaintiffs in that litigation (*Chelius et al v. Becerra*, Joint Mot. to Stay Case Pending Agency Review, ECF No. 148, May 7, 2021, Civ. No. 1:17-00493 (D. Haw.)).

<sup>11</sup> Although we have determined that the Mifepristone REMS Program must be modified to add a requirement for pharmacy certification, this was not raised in your Petition and therefore is not discussed further in this response.



Docket No. FDA-2019-P-1534

- Adding a requirement that pharmacies that dispense the drug be specially certified.

## II. DISCUSSION OF ISSUES RAISED

### A. Mifeprex Regimen

#### 1. Indications and Usage

In the Petition, you ask FDA to restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to limit Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, to 49 days gestation (Petition at 1 and 3). For the reasons explained below, we deny this request.

Citing to a 2011 study and a practice bulletin issued by the American College of Obstetricians and Gynecologists (ACOG), you state that medical abortion<sup>12</sup> regimens demonstrate an increase in complications and failures, including serious risks of hemorrhage, infection, and ongoing pregnancy, after 49 days gestation (Petition at 3-4).

Our review of the S-020 efficacy supplement in 2016 concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.<sup>13</sup> Complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of Mifeprex (with an indication for medical termination of intrauterine pregnancy through 49 days gestation) were 92.1 percent and 95.5 percent in the United States and French trials, respectively.<sup>14</sup> The studies reviewed in support of the 2016 approval for Mifeprex (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 Clinical Review of the S-020 efficacy supplement summarized clinical outcomes and adverse effects from 22 studies (7 in the United States and 15 from outside the United States) through 70 days gestation, using the currently approved regimen of 200 mg oral mifepristone with 800 mcg buccal misoprostol. The ranges of complete medical abortion rates calculated by the clinical reviewer were 93.2 percent to 98.7 percent in the United States studies, and 92 percent to 98 percent in the non-United States studies.<sup>15</sup>

Serious adverse events associated with the use of mifepristone through 70 days gestational age are rare. Per the current mifepristone labeling, the rates of serious adverse events are low: transfusions are 0-0.1 percent, sepsis is less than 0.01 percent, hospitalization related to medical abortion is 0-0.7 percent, and hemorrhage is 0.1 percent.<sup>16</sup> As discussed

---

<sup>12</sup> In this response, the terms “medical abortion” and “medication abortion” both refer to the use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy.

<sup>13</sup> See 2016 Clinical Review available at

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/020687Orig1s020MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf), at 32-38 and 47-47.

<sup>14</sup> See 1999 Medical Officer’s Review, available at

[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/20687\\_Mifepristone\\_medr\\_P1.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf), at 11 (Table 1) and 16.

<sup>15</sup> See 2016 Clinical Review, *supra* n. 13, at 28-31.

<sup>16</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

Docket No. FDA-2019-P-1534

throughout this response, the benefit/risk assessment supported our 2016 conclusion that the product is safe and effective through 70 days gestation.

In support of your assertion that medical abortion demonstrates an increase in complications after 49 days gestation, you cite to Mentula, et al.,<sup>17</sup> a register-based, retrospective cohort study that included 18,248 women in Finland who underwent medical abortion between January 1, 2003, and December 31, 2006 (Petition at 3). As an initial matter, we note that the Mentula study was primarily designed to assess the immediate adverse events following medical abortion in the second trimester (13 to 24 gestational weeks as defined by the authors) and then compare those events to those identified with medical abortion in the first trimester (up to 12 gestational weeks as defined by the authors). The study was not designed to compare rates of complications across gestational weeks within the first trimester. It is true that the Mentula publication includes information on the percentages of women who had surgical evacuation following medical abortion and the percentages of women who had infection following medical abortion, based on weekly gestational age, from 5 weeks to 20 weeks gestation.<sup>18</sup> However, the data in the Mentula study are relatively old (2003-2006); in our 2016 review of the S-020 efficacy supplement, we conducted an extensive review of more recent data<sup>19</sup> and concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.

You also cite to ACOG Practice Bulletin No. 143, which states: “the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days.”<sup>20</sup> This statement is based on a 1998 publication which evaluated patients undergoing medical abortion with mifepristone 600 mg and then oral misoprostol 400 mcg two days later.<sup>21</sup> The regimen studied in this 1998 publication is not the currently approved regimen for mifepristone in the United States. Further, ACOG Practice Bulletin No. 143 has been withdrawn and replaced by Practice Bulletin No. 225, which was published in October 2020 and no longer contains this statement.<sup>22</sup>

You also state that the failure rate of the approved regimen (which you refer to as the “buccal misoprostol regimen”) increases as the gestational age increases, especially at

<sup>17</sup> Mentula MJ, Niinimake M, Suhonen S, et al. Immediate Adverse Events After Second Trimester Medical Termination of Pregnancy: Results of a nationwide registry study, *Human Reproduction*. 2011;26(4):927-932.

<sup>18</sup> *Id.* at Fig. 2 and Fig. 3. Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of abortion completion rates accounts for the need for surgical intervention. In clinical studies we reviewed, success of medical abortion was defined as the complete expulsion of the products of conception without the need for surgical intervention.

<sup>19</sup> See 2016 Cross-Discipline Team Leader Review, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/020687Orig1s020CrossR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf), at 37 (Table 4).

<sup>20</sup> Petition at 3. See Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); *Obstet Gynecol*. 2014 Mar;123(3):676-692 at 680.

<sup>21</sup> Spitz I, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States, *NEJM*. 1998;338 (18):1241-1247.

<sup>22</sup> See ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. *Obstetrics and Gynecology* 2020; 136(4); e31 to e47.

Docket No. FDA-2019-P-1534

gestational ages greater than 49 days, relying on a 2015 meta-analysis,<sup>23</sup> and that the gestational limit should not have been increased (Petition at 3-4). We agree that the failure rate of medical abortion regimens, including the currently approved regimen, generally increases with increasing gestational age. However, the increase in failure rate with each incremental week of gestation, as described in approved mifepristone labeling and in this 2015 meta-analysis, is small, and we believe that the benefit/risk profile for medical termination of intrauterine pregnancy between 49 and 70 days gestation remains acceptable.

For these reasons, we deny your request that FDA limit mifepristone, in a regimen with misoprostol for the termination of intrauterine pregnancy, to 49 days gestation.

## 2. Dosage and Administration

### a. Prescriber Qualifications

You state that FDA should limit the “ability” to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than permitting non-physicians to apply to be certified prescribers, because of the regimen’s serious risks and because physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age (Petition at 4). We do not agree.

Healthcare providers who are licensed to prescribe can become certified in REMS programs if they are able to meet the applicable REMS requirements. To become certified to prescribe mifepristone under the Mifepristone REMS Program, the prescriber must review the prescribing information for mifepristone and complete a Prescriber Agreement Form. By signing the form, the prescriber agrees that they meet certain qualifications, including the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also: (1) be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care; or (2) be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.<sup>24</sup>

In our review of the S-020 efficacy supplement in 2016, we determined that available data support that Mifeprex is safe and effective when prescribed by midlevel providers, such as physician assistants and nurse practitioners, as well as by physicians.<sup>25</sup> Our 2016 review included four studies that evaluated the safety and efficacy of medical abortion when performed by non-physician healthcare providers. Two trials evaluated the currently

<sup>23</sup> Petition at 4, fn. 6 (citing Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, *Obstet. Gynecol* 126 (1) July 2015 12-21).

<sup>24</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf); see also <https://www.accessdata.fda.gov/scripts/cder/remes/index.cfm?event=RemsDetails.page&REMS=390>.

<sup>25</sup> See 2016 Clinical Review, supra n. 13, at 79; see also 2016 Cross-Discipline Team Leader Review, supra n. 19, at 17-18. We also note that in most states, midlevel clinicians, such as physician assistants and nurse practitioners, are licensed to prescribe medications.



Docket No. FDA-2019-P-1534

approved Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner);<sup>26,27</sup> one trial studied a regimen using vaginal misoprostol (Warringer);<sup>28</sup> a fourth study did not specify the route of misoprostol administered (Puri).<sup>29</sup> Olavarrieta reported a completion rate of 97.9 percent when medical abortion was provided by nurses as compared with 98.4 percent with physicians. Kopp Kallner reported a completion rate of 99 percent with certified nurse midwives versus 97.4 percent with physicians. Warriner reported an abortion completion rate of 97.4 percent with nurses as compared with 96.3 percent with physicians. Puri reported an abortion completion rate of 96.8 percent when the service was provided by nurse-midwives as compared with 97.4 percent in the “standard care” group.<sup>30</sup> Our 2016 review also included a systematic review of six controlled clinical studies by Renner;<sup>31</sup> the authors concluded that the evidence “indicates that trained mid-level providers may effectively and safely provide first trimester surgical and medical termination of pregnancy services.” Additionally, Barnard et al., in a Cochrane systematic review, assessed the safety and effectiveness of abortion procedures administered by mid-level providers (nurse practitioners, midwives, other non-physician healthcare providers) compared to doctors.<sup>32</sup> The authors concluded, based in part on two of the studies that we had reviewed in 2016,<sup>33</sup> that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors.

We also believe that the identification of patients for whom the use of mifepristone is contraindicated can be done by mid-level healthcare providers, as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:<sup>34</sup>

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass

<sup>26</sup> Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus Physician-provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial. *Bull World Health Organ.* 2015;93:249-258.

<sup>27</sup> Kopp Kallner H, Gomperts R, Salomonsson E, et al. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. *BJOG.* 2015; 122: 510-517.

<sup>28</sup> Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. *Lancet.* 2011; 377: 1155-61.

<sup>29</sup> Puri M, Tamang A, Shrestha P, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. *Reproductive Health Matters.* 2015; 22(44) 94-103.

<sup>30</sup> 2016 Clinical Review, supra n. 13, at 43.

<sup>31</sup> Renner RM, Brahma D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. *BJOG* 2013 Jan;120(1):23-31.

<sup>32</sup> Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). *Cochran Database of Systematic Reviews.* 2015, Issue 7.

<sup>33</sup> Of the medical abortion studies reviewed by Barnard et al (Id.), two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al (supra n. 28) and Kopp Kallner et al (supra n. 27). The third used a different dose of misoprostol than the currently approved regimen. See Jejeebhoy SJ, Kalyanwalaa S, Zaviera AJF, Kumara R, Mundleb S, Tank J, et al. Feasibility of expanding the medication abortion provider based in India to include ayurvedic physicians and nurses. *International Perspectives on Sexual and Reproductive Health* 2012;38(3)133-42)

<sup>34</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

Docket No. FDA-2019-P-1534

- An intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandins
- Hemorrhagic disorder or concurrent anticoagulant therapy
- Inherited porphyrias

These contraindications can be assessed by trained healthcare providers who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. We continue to believe that available data support the conclusion that mid-level healthcare providers, as well as physicians, possess the clinical and counseling skills necessary to provide medical abortion. We note this is consistent with ACOG’s statement in its current practice bulletin that “[i]n addition to physicians, advanced practice clinicians, such as nurse-midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion.”<sup>35</sup> Further, if necessary, ultrasound training and certification is available to nurse practitioners and physician assistants, as well as physicians.<sup>36</sup> In sum, available information supports that mid-level healthcare providers as well as physicians can determine whether mifepristone is an appropriate treatment for a particular patient and dispense it.

You also assert that FDA should strengthen the requirement that providers accurately assess the duration of the pregnancy by mandating that gestational age be assessed by ultrasound (Petition at 5). We refer you to FDA’s 2016 Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (the “2016 CP Response”), where FDA stated that the determination of gestational age does not always require an ultrasound. In the 2016 CP Response, FDA stated it had “determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS [transvaginal ultrasound]) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider.”<sup>37</sup>

In the Petition, you reference the Prescriber Agreement Form, in which the provider must attest they have the ability to: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed (or have made plans to provide such care through others), and you state that a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional

---

<sup>35</sup> ACOG Practice Bulletin No. 225, *supra* n. 22.

<sup>36</sup> American Institute of Ultrasound in Medicine. Accessed November 26, 2021. <https://www.aium.org/officialStatements/70>.

<sup>37</sup> FDA’s citizen petition response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical and Dental Association, and Concerned Women for America on August 20, 2002, Docket No. FDA-2002-P-0364 at 18. See <https://www.regulations.gov/document/FDA-2002-P-0364-0002>.

Docket No. FDA-2019-P-1534

contraindications (Petition at 5-6). You state that FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4).

Certified prescribers do not have to be physically present with the patient as long as they have confirmed the patient's gestational age and intrauterine pregnancy. As noted above, in the 2016 CP response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."<sup>38</sup> Moreover, the evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber and can be done in different types of healthcare settings. A certified prescriber can also review the Patient Agreement Form<sup>39</sup> with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity. See also section II.B.1.c (ETASU C – In-person Dispensing).

With respect to providing surgical intervention in cases of incomplete abortion or severe bleeding and assuring patient access to medical facilities equipped to provide blood transfusions and resuscitation (if necessary), the Prescriber Agreement Form does not reflect a requirement that the certified prescriber must provide such care personally; rather, the prescriber must agree that they have the ability to provide such care or that they have made plans to provide such care through others, and that they have the ability to assure the patient has access to appropriate medical facilities. It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients, and in many places, hospitals employ "hospitalists" to provide care to all hospitalized patients. We also note ACOG's statement that "[i]n rare cases, a patient who undergoes a medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral."<sup>40</sup>

For these reasons, we deny your request that FDA limit the "ability" to prescribe and dispense mifepristone to licensed physicians, and we deny your request that FDA require certified providers to physically meet with and examine the patient.

#### **b. Office Visits and Administration of Mifepristone/Misoprostol**

In the Petition, you state that the use of mifepristone and misoprostol should require three office visits by the patient (Petition at 7). In support of this position, you state the following:

- Drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10).

---

<sup>38</sup> Id.

<sup>39</sup> See <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>.

<sup>40</sup> ACOG Practice Bulletin Number 225 supra n. 22.



Docket No. FDA-2019-P-1534

- Abortion complications are more frequent when women abort at home and more healthcare oversight is needed (Petition at 8).
- Home administration of misoprostol does not permit healthcare providers to control when their patients take misoprostol and without monitoring:
  - a patient may take buccal misoprostol before the minimum 24-hour period after taking Mifeprex, which leads to a significantly increased failure rate (Petition at 7).
  - a patient may swallow misoprostol rather than administer it buccally, and oral administration is not as effective as buccal administration in ending the pregnancy (Petition at 7).
- Because providers may now “confirm” that a patient’s drug-induced abortion was successful without a clinic visit, this increases the threat that Rh-negative patients will not receive Rhogam, which is necessary to prevent serious risks in subsequent pregnancies (Petition at 7 and 9).

We address each of these points below.

#### **i. Follow-up Care**

The safe use of mifepristone when used in the approved regimen with misoprostol is not contingent on a specific number of office visits being made by the patient undergoing a medical termination of pregnancy. The 2016 labeling change for Mifeprex regarding post-treatment assessment, including the change to the approved regimen to reduce the number of office visits from three to one, was based on evidence reviewed in the S-020 efficacy supplement. We concluded, upon reviewing the data, that three office visits were not necessary to assure the safe use of Mifeprex.<sup>41</sup>

In your Petition, you point to statements by ACOG that medical abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 8, 10). The ACOG statements you point to are from ACOG Practice Bulletin No. 143, which has been withdrawn and replaced by Practice Bulletin No. 225.<sup>42</sup> Neither of the statements from the withdrawn Practice Bulletin nor Practice Bulletin No. 225 contraindicate medical abortion in women who are not available for an in-clinic follow-up visit. The current ACOG recommendations indicate that for medical abortion, “[f]ollow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility.”<sup>43</sup> The patient and their healthcare provider should determine the best option for follow-up as part of the consultation and consent process.<sup>44</sup> As reflected in ACOG’s guidance, appropriate follow-

---

<sup>41</sup> See 2016 Clinical Review, *supra* n. 13, at 44 and 64-67.

<sup>42</sup> ACOG Practice Bulletin Number 225, *supra* n. 22.

<sup>43</sup> *Id.*

<sup>44</sup> *Id.*

Docket No. FDA-2019-P-1534

up after medical termination of a pregnancy may be accomplished in multiple ways and not all require an in-clinic visit.

You also question findings in multiple studies that evaluated the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, or MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies and assessed the ability of patients to self-administer these tests and interpret the test results (Petition at 9-10). Overall, these studies concluded that in the majority of women, it is feasible to use a simplified test to determine if further follow-up is necessary. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion completed at home versus routine clinic follow-up after medical abortion, concluding self-assessment was not inferior to routine clinic follow-up.<sup>45</sup> We note that this is consistent with current ACOG recommendations, which state that “follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility.”<sup>46</sup>

You also assert that it is important for a patient to be under observation after taking misoprostol to ensure that they are appropriately monitored and provided sufficient pain medication (Petition at 8). You cite the World Health Organization (WHO)’s statement in guidance that up to 90 percent of women will abort within 4-6 hours after taking misoprostol; you further state that the 2000 regimen permitted patients to be in the clinic during this time period (Petition at 8). Your reference to the WHO guidance document<sup>47</sup> appears to be out of context. The WHO guidance takes no position on whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol; in fact, it explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.<sup>48</sup> In the United States, and as reflected in the approved labeling, medical termination of pregnancy usually involves patients terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

#### ii. At Home Medical Abortion and Healthcare Oversight

In addition, you cite a 2018 study to support your statement that abortion complications are more frequent when women abort at home (Petition at 8). The study evaluated complications following medical abortion (both less than 12 weeks and more than 12 weeks gestation) as well as following surgical abortion, at one hospital in Sweden between 2008 and 2015.<sup>49</sup> For the years 2008 to 2010, data were collected retrospectively; for the years

---

<sup>45</sup> Baiju, N, Acharya, G, D’Antonio, F, et al. 2019. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. *BJOG*; 126:1536-1544.

<sup>46</sup> ACOG Practice Bulletin Number 225, supra n. 22.

<sup>47</sup> World Health Organization, *Safe Abortion: technical and policy guidance for health systems – 2<sup>nd</sup> edition*. 2012. Page 45 and Section 2.2.2.1 Medication for pain.

<sup>48</sup> *Id.* at Section 2.3 Post-abortion care and follow-up, at 52.

<sup>49</sup> Carlsson I, Breding K, Larsson PG, 2018, Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study, *BMC Women’s Health* 18:158.

Docket No. FDA-2019-P-1534

2011 to 2015, data were collected prospectively. In this study, medical abortions after 12 gestational weeks all occurred at the hospital. The authors report that, among medical abortions less than 12 weeks, the complication frequency increased from 5.4 percent (2008 to 2010) to 8.2 percent (2015). However, the authors also compared the complications related to medical abortions that occurred at less than 12 gestational weeks between “at home” abortions (managed as an outpatient) and “at the hospital” abortions, in 2015 and found no statistically significant difference (8.2 percent “at home” versus 8.0 percent at the hospital). For pregnancies less than or equal to 9 gestational weeks, the rates are similar for the “at home” group (10.0 percent) and the “at the hospital” group (9.3 percent). Notably, as part of our review and approval of the S-020 efficacy supplement in 2016, we assessed serious adverse events by gestational age, including hospitalizations, serious infection requiring hospitalization or intravenous antibiotics, bleeding requiring transfusion, and ectopic pregnancy, as reported in the literature submitted by the Applicant. We concluded that these serious adverse events are rarely reported in the literature and that the regimen of mifepristone 200 mg followed by buccal misoprostol 800 mcg in 24-48 hours is safe to approve for use through 70 days gestation.<sup>50</sup>

You also state that medical abortion is a longer process than surgical abortion and that it requires more attention and care from healthcare providers (Petition at 10). We agree that medical abortion can be a longer process than surgical abortion,<sup>51</sup> but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. Not all of the complications associated with medical abortion necessarily require more intensive management from healthcare providers during a follow-up visit. The question of whether to include an in-person follow-up visit should be discussed by the healthcare provider and the patient. We have concluded that medical abortions are safe and effective for patients who are appropriate candidates and reducing the number of clinic visits does not compromise patient safety.

The current approved labeling for mifepristone for medical termination of pregnancy states that complete pregnancy termination “can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan.” Not all these modalities require an in-clinic assessment during a follow-up visit. Our review of the S-020 efficacy supplement concluded that “available data support ... that there are a variety of follow-up modalities that can adequately identify the need for additional intervention.”<sup>52</sup> We note that these findings are also consistent with ACOG guidelines, which state that “[r]outine in-person follow-up is not necessary after uncomplicated medication abortion” and recommend several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at one week after treatment followed by urine pregnancy testing at four weeks after treatment.<sup>53</sup> Because there is more than one effective method to detect an on-going pregnancy, we conclude that the way in which post-treatment follow-up is performed may be determined by the healthcare provider and the patient.

<sup>50</sup> 2016 Clinical Review, *supra* n. 13, at 51-57.

<sup>51</sup> See ACOG Practice Bulletin Number 225, *supra* note 22.

<sup>52</sup> 2016 Cross Discipline Team Leader Review, *supra* n. 19, at 17.

<sup>53</sup> ACOG Practice Bulletin Number 225, *supra* note 22.



Docket No. FDA-2019-P-1534

### iii. Misoprostol

In the Petition, you make a number of assertions regarding the use of misoprostol. We address each in turn.

First, you assert that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex, thereby rendering the regimen ineffective, and that home administration of misoprostol does not permit health providers to control when their patients take misoprostol (Petition at 7). You similarly assert that the use of buccal misoprostol sooner than 24 hours after administering mifepristone leads to significantly increased failure rates (Petition at 7).

As an initial matter, our review of the S-020 efficacy supplement in 2016 included data that evaluated the home use of misoprostol in over 30,000 women. The data showed that Mifeprex was safe and effective in a regimen with misoprostol when misoprostol was self-administered at home.<sup>54</sup> Therefore, any incorrect administration resulting in a failed abortion was infrequent and did not significantly affect the safety and efficacy of medical abortion. Furthermore, because the process of expelling the pregnancy may begin as soon as 2 hours after taking misoprostol, there is a benefit in allowing patients to choose when and where to start this process, to maximize the possibility of their being at a safe place at a convenient time to experience cramping and bleeding.<sup>55</sup>

In support of your assertion of significantly increased failure rates, you cite a pilot study by Lohr et al.<sup>56</sup> Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (less than or equal to 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations<sup>57</sup> using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates reported by Lohr at 24 hours for oral mifepristone and buccal misoprostol were 72.5 percent, 69.2 percent, and 72.5 percent, respectively; the complete abortion rates at two weeks, however, were 97.5 percent, 100 percent, and 94.9 percent, respectively (and are consistent with the completion rates as described in the approved labeling).<sup>58</sup> The published complete abortion rates at 24 hours for simultaneous oral mifepristone and vaginal misoprostol administration were 90 percent, 88 percent, and 83 percent, respectively, for the gestational age groupings and the complete abortion rates at 2 weeks were 98 percent, 93 percent, 90 percent, respectively. Based on the data presented in Lohr,

<sup>54</sup> See 2016 Clinical Review, *supra* n. 13, at 41 and 48.

<sup>55</sup> *Id.* at 38.

<sup>56</sup> Petition at 7 (referencing Lohr PA, Reeves MF, Hayes JL, et al., 2007, Oral Mifepristone and Buccal Misoprostol Administered Simultaneously for Abortion: A Pilot Study, *Contraception*, 76:215-220).

<sup>57</sup> Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. *Contraception* 2005;71:447-50; Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. *Contraception* 2005;71:333-6.

<sup>58</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

Docket No. FDA-2019-P-1534

the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. As recommended in Section 2.3 of the approved labeling, follow-up at 7-14 days after administration of mifepristone is more appropriate to evaluate efficacy.<sup>59</sup> It is misleading to only reference the abortion completion rates observed at the 24-hour timepoint from Lohr. Therefore, we do not agree that data from Lohr indicate higher failure rate with misoprostol taken before the prescribed minimum 24-hour period after taking mifepristone.

Although we disagree that Lohr demonstrates a higher failure rate with misoprostol taken before 24-hours after taking mifepristone, we note that our 2016 review of the S-020 efficacy supplement referenced a 2013 systematic review by Raymond, which concluded that if the interval between mifepristone and misoprostol interval is less than or equal to 24 hours, the procedure is less effective compared to an interval of 24-48 hours.<sup>60</sup> As explained above, the data reviewed in 2016 showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective. Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. However, in light of the data reviewed, section 2.1 of the labeling approved in 2016 (as well as the currently approved labeling and Medication Guide) states that there should be a “minimum 24-hour interval between” mifepristone and misoprostol (emphasis included in the labeling).<sup>61</sup> The approved dosing regimen also states that misoprostol is taken within 24 to 48 hours after taking mifepristone and acknowledges that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration.

In addition to your concerns that a woman may take misoprostol too soon after administering mifepristone, you also state that waiting until 24 hours after administering mifepristone does not guarantee success (Petition at 7-8). In support of this concern, you cite a 2015 review by Chen and Creinin. You state that this review found “women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen” (Petition at 8). Chen and Creinin included studies in which the intervals between mifepristone and buccal misoprostol were 24 hours or 24-48 hours and stated that “based on the available literature, the overall efficacy of regimens with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2 percent compared with 96.8 percent).”<sup>62</sup> The rate differences were statistically significant, but both regimens were more effective than the 92 percent efficacy rate of the original regimen approved in 2000 (administering misoprostol 48 hours after taking mifepristone).

Finally, you also express concern that if misoprostol is self-administered, a woman may swallow it rather than keep the pill between her cheek and gum, and oral administration of

---

<sup>59</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

<sup>60</sup> 2016 Clinical Review, supra n. 13, at 31 (citing 8 Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87(1):26-37.)

<sup>61</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

<sup>62</sup> See Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. *Obstet Gynecol.* 2015;126(1):12-21; see also 2016 Clinical Review, supra n. 13, at 21.

Docket No. FDA-2019-P-1534

misoprostol (i.e., swallowing the pill) following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy (Petition at 7). Winikoff et al. specifically studied the use of oral compared to buccal misoprostol 24-36 hours after mifepristone 200 mg with overall success rates of 91.3 percent and 96.2 percent, respectively.<sup>63</sup> Both regimens resulted in a greater than 91 percent successful medical abortion. Although the study showed decreased efficacy with oral versus buccal administration in 57-63 days gestational age, there were no statistical differences in other gestational age groupings. Even assuming there is a small proportion of women who are 57-63 days gestational age and use oral administration of misoprostol (rather than buccal as labeled), a small decrease in the reported efficacy in that population would not justify requiring a clinic visit for all women undergoing medical abortion.

Overall, studies support the efficacy of the mifepristone, in a regimen with misoprostol when taken by the patient at home. Therefore, we do not agree that an in-person visit is necessary to manage administration of misoprostol.

### iii. Rh-Negative Patients

In the Petition, you state that a follow-up examination is particularly critical for Rh-negative patients and that without that follow-up examination, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9). You suggest that a clinic visit after the administration of Mifeprex is important for Rh-negative women to receive Rhogam and that removing the required follow-up visit puts Rh-negative women at risk for isoimmunization. We do not agree.

Rh testing is standard of care in the United States and RhD immunoglobulin (such as Rhogam) should be administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).<sup>64</sup> However, the facility where the RhD immunoglobulin injection occurs (clinic, hospital or laboratory) is not critical. A shift from medical clinics to hospitals for administration of injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.<sup>65</sup> This has resulted in pregnant women frequently obtaining routine 28-week RhD immunoglobulin injections at hospitals/laboratories with a prescription provided by their healthcare providers. This same process of obtaining RhD immunoglobulin via prescription is available to patients after medical termination of pregnancy and does not require a follow-up clinic visit.

---

<sup>63</sup> Winikoff B, Dzuba, IG, Creinin MD, et al, 2008, Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion, *Obstet Gynecol* 112(6):1303-1310.

<sup>64</sup> ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.

<sup>65</sup> See <https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers>.



Docket No. FDA-2019-P-1534

In summary, the totality of data on the efficacy and safety of medical abortion at less than 70 days gestation, derived from numerous studies, has characterized the complications and rates of complications for completing medical abortion at home, and the findings show medical abortion at home is both safe and effective without three office visits. We therefore deny your request that the use of mifepristone in a regimen with misoprostol require three office visits by the patient.

### c. Contraindications

In the Petition, you assert that critical language contraindicating Mifeprex for patients without access to appropriate emergency medical care was excluded from the 2016 Mifeprex labeling. You cite to a study<sup>66</sup> and ACOG statements as evidence that medical abortions have greater risks and more need for emergency “operation” than a surgical abortion, particularly for patients in rural areas with limited access to emergency medical care (Petition at 11).

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in section 4 of the approved labeling when we approved the S-020 efficacy supplement, the 2016 Mifeprex labeling and the currently approved mifepristone labeling, as well as the Mifepristone REMS Program, continue to include appropriate instructions for providers regarding patient access to appropriate medical care.<sup>67</sup> For example, the Boxed Warning includes language directing healthcare providers to ensure that the patient knows whom to call and what to do, including potentially going to an emergency room, if the patient experiences serious events associated with the use of mifepristone. The labeling also directs healthcare providers, as part of the dosing regimen, to give the patient the name and phone number of a healthcare provider who will be handling emergencies.<sup>68</sup> In addition, one of the required qualifications listed in the Prescriber Agreement Form is the “[a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.”<sup>69</sup> Therefore, although certain language about access to medical facilities was removed from the approved labeling in 2016, we disagree that critical language about access to appropriate emergency medical care is lacking from the approved labeling.

<sup>66</sup> See Petition Reference Document No. 17 (Harrison Affidavit: Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015), ¶115 (referencing M. Niinimäki et al., Immediate Complications after Medical compared with Surgical Termination of Pregnancy, *Obstet. Gynecol.* 114:795 (Oct. 2009)).

<sup>67</sup> See Mifeprex labeling, approved 2016.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf). See also current labeling at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

<sup>68</sup> Id.

<sup>69</sup> Mifepristone REMS Program,

<https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>. Emphasis added.

Docket No. FDA-2019-P-1534

You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.<sup>70</sup> As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

**d. Adverse Event Reporting**

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

---

<sup>70</sup> Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.

Docket No. FDA-2019-P-1534

You state that FDA should provide guidance to emergency healthcare providers and physicians so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13). We disagree that specific guidance is needed at this time. In the past, when appropriate, FDA has worked with the NDA Applicant to issue communications to healthcare providers and emergency department providers concerning certain serious adverse events.<sup>71</sup> Furthermore, the approved Medication Guide advises patients to take the Medication Guide with them if they need to go to the emergency room or seek care from a healthcare provider other than the one who dispensed the medication to them, so the emergency room or healthcare provider understands the patient is having a medical abortion. We have not identified a change in the safety profile of mifepristone that would warrant additional communications to healthcare providers and emergency department providers concerning complications following medical abortion. If we become aware of safety information that merits further communications with emergency department providers or healthcare providers, or that warrants revisions to the approved labeling, we will act as appropriate.

You also assert that many Mifeprex prescribers “violate FDA protocol,” instructing their patients to lie to emergency medical personnel, and that this prevents emergency healthcare providers from appropriately caring for their patients and further decreases the likelihood that adverse events will be reported (Petition at 12). Your only support for this claim is a reference to instructions from the organization Aid Access<sup>72</sup> to patients that they can tell emergency room staff that they had a miscarriage and do not need to tell medical staff that they had a medical abortion. The Petition does not provide any data or additional information establishing “many Mifeprex prescribers violate FDA protocol, instructing their patients to lie,” or that these providers thereby prevented appropriate care and decreased the number of adverse events reported.

## **B. REMS**

### **1. Request to Retain Mifeprex REMS**

In your Petition, you request that FDA retain the Mifeprex REMS (Petition at 14). We agree that a REMS is necessary to ensure that the benefits of mifepristone in a regimen with misoprostol outweigh the risks. FDA’s determination as to whether a REMS is necessary

---

<sup>71</sup> See Historical Information on Mifepristone (Marketed as Mifeprex), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm>. For example, the NDA applicant and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 and a Dear Emergency Room Director letter in September 2004. The fact that these letters were issued does not imply that the approved mifepristone regimen is unsafe; it is not uncommon for drug sponsors to issue “Dear Health Care Provider” letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, “[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely.”

<sup>72</sup> We note that Aid Access facilitated the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA sent Aid Access a warning letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers. US FDA Warning Letter to Aidaccess.org, dated March 8, 2019. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019>.



Docket No. FDA-2019-P-1534

to ensure that the benefits of a drug outweigh its risks is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case.<sup>73</sup> In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.<sup>74</sup>

As described in the background section of this response (see section I.A.), FDA determined that interventions in addition to the FDA-approved labeling were necessary to ensure that the benefits of Mifeprax outweighed its risks when the drug was initially approved in 2000, and periodic re-evaluations of the REMS since that time have reached the same conclusion. As further described in the background section of this response (see section I.E.), FDA recently undertook a review of the Mifepristone REMS Program. As explained below, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risks.

After review of multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FAERS reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation,<sup>75</sup> as well as information submitted by the Applicants, we have concluded that the REMS can be modified to reduce the burden on the health care delivery system without compromising patient safety. As explained below, we agree that the healthcare provider certification (ETASU A) and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions (ETASU D) continue to be necessary components of the REMS to ensure the benefits outweigh the risks. However, we have concluded that the Mifepristone REMS Program must be modified to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

Below, we discuss each of these elements of the Mifepristone REMS Program.

**a. ETASU A – Prescriber Certification/Qualifications**

ETASU A under the Mifepristone REMS Program requires healthcare providers who prescribe mifepristone to be certified. In order to become certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the Prescriber Agreement Form. In signing the Prescriber Agreement Form, prescribers agree they meet the qualifications listed below:

---

<sup>73</sup> See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Apr. 2019).

<sup>74</sup> *Id.*

<sup>75</sup> See *supra* n. 10.

Docket No. FDA-2019-P-1534

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

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

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

Our review of the published literature did not identify any studies comparing healthcare providers who met these qualifications with healthcare providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention either personally or through others, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our conclusion continues to be that a healthcare provider who prescribes mifepristone in a regimen with misoprostol should meet the above qualifications. Absent these provider qualifications, we are concerned that serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, may not be detected or appropriately managed.

Accordingly, we have determined that ETASU A must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks. Maintaining the requirement for prescriber certification ensures that providers meet the necessary qualifications and adhere to the guidelines for use listed above. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one-time for each applicant.

Docket No. FDA-2019-P-1534

Although we agree with your request to retain the REMS for mifepristone (now the Mifepristone REMS Program) insofar as it pertains to ETASU A, as discussed in section II.A.2.a of this response, we do not agree with your request that the healthcare provider needs to be a licensed physician to meet this requirement.

**b. ETASU D – Requirement For The Drug To Be Dispensed With Evidence Or Other Documentation Of Safe-Use Conditions**

ETASU D under the Mifepristone REMS Program requires mifepristone to be dispensed with evidence or other documentation of safe-use conditions. To receive mifepristone for medical termination of intrauterine pregnancy through 70 days gestation, the patient must sign a Patient Agreement Form indicating that the patient has received, read, and been provided a copy of the Patient Agreement Form and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The Patient Agreement Form ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication. In a number of approved REMS, Patient Agreement Forms or Patient Enrollment Forms ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.<sup>76</sup>

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

In addition, we conducted an updated review of published literature since 2016 to assess the utility of maintaining the Patient Agreement Form as part of the Mifepristone REMS Program, and these studies do not provide evidence that would support removing ETASU D. For these reasons, we have determined that ETASU D must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks.

---

<sup>76</sup> REMS@FDA, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>, Accessed November 15, 2021.



Docket No. FDA-2019-P-1534

**c. ETASU C – In-Person Dispensing**

ETASU C under the Mifepristone REMS Program currently requires mifepristone to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. This creates what we refer to in this response as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office, or hospital when the drug is dispensed. The mifepristone REMS document currently states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than a clinic, medical office, or hospital. As explained below, based on a recent review of the REMS, we believe that the Mifepristone REMS Program must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks. This conclusion is based on our review of information from the Mifepristone REMS Program one-year (1<sup>st</sup>) REMS<sup>77</sup> assessment data and postmarketing safety information, and supported by our review of the published literature.

**i. Assessment Data**

As part of our review of the REMS, we evaluated information included in the 1<sup>st</sup> REMS assessment report for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, and non-compliance data. This 1<sup>st</sup> REMS assessment report covers a reporting period between April 11, 2019 through February 29, 2020. During this reporting period, a small number of non-compliance events were reported.

As described in section I.C. of this response, during the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not enforced. To better understand whether there was any impact on safety or non-compliance during the periods when the in-person dispensing requirement was not enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or non-compliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. The NDA and the ANDA Applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no

---

<sup>77</sup> This REMS assessment report was the first submitted following the approval of the single, shared system REMS for mifepristone.

Docket No. FDA-2019-P-1534

indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events.

ii. FAERS/Postmarketing Safety Data

FDA routinely monitors postmarketing safety data for approved drugs through adverse events reported to our FAERS database,<sup>78</sup> through our review of published medical literature, and when appropriate, by requesting applicants submit summarized postmarketing data. For our recent review of the REMS, we searched our FAERS database, reviewed the published medical literature for postmarketing adverse event reports for mifepristone for medical termination of pregnancy, and requested that the Applicants submit a summary and analysis of certain adverse events. Our review of this postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced.

In order to evaluate the periods when in-person dispensing was and was not enforced, we conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy. The data for this time period were then further divided into the date ranges when in-person dispensing was enforced per the REMS (January 27, 2020 - July 12, 2020 and January 13, 2021 - April 12, 2021) versus when in-person dispensing was not enforced: July 13, 2020 - January 12, 2021 (in-person dispensing enforcement was temporarily enjoined) and April 13, 2021 - September 30, 2021 (enforcement discretion for in-person dispensing because of the COVID-19 PHE).

Based on the above search, a total of eight cases were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when in-person dispensing was being enforced (i.e., January 27, 2020-July 12, 2020 and January 13, 2021-April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when in-person dispensing was not enforced (i.e., July 13, 2020-January 12, 2021 and April 13, 2021-September 30, 2021); however, the narratives provided in the FAERS reports for three of the five cases explicitly stated that mifepristone was dispensed in-person. These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Of note, ongoing pregnancy and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case reported the occurrence of oral pain/soreness (case 8) in July

---

<sup>78</sup> FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

Docket No. FDA-2019-P-1534

2021, but did not provide sufficient information to determine the exact date of the adverse event.

As discussed in section II.A.2.d., the Applicants report adverse events, including serious adverse events, to FDA in accordance with applicable regulations.<sup>79</sup> To enable additional review of adverse events, Applicants were requested to provide a summary and analysis for adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided the requested summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021. The Applicant for the generic provided the requested summary of postmarketing safety information from April 11, 2019 (date of initial approval) through September 30, 2021. The information provided by the Applicants included the same cases identified in FAERS, as discussed above.

We analyzed the FAERS data referenced above to determine if there was a difference in adverse events when in-person dispensing was and was not enforced. Based on FDA's review of this data, we concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced and that mifepristone may be safely used without in-person dispensing. FDA's review of the summary and analysis data submitted by the Applicants (which, as noted above, included the same cases identified from FAERS) did not change this conclusion.

### iii. Published Literature

As noted above, we also conducted an extensive review of the published literature since March 29, 2016 (the date the S-020 efficacy supplement for Mifeprex was approved) through September 30, 2021.<sup>80</sup> Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or equivalent healthcare provider in countries other than the United States). Some studies have examined replacing in-person dispensing in certain healthcare settings with dispensing at retail pharmacies<sup>81</sup>

<sup>79</sup> See 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81.

<sup>80</sup> In support of your request that we retain the REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber, you reference two studies that you assert do not comply with the REMS (Petition at 19-22). Outcomes from both of the studies you reference have been reported in the published literature and are addressed in the discussion that follows. We note that as a general matter, a clinical investigation of an approved drug that is subject to a REMS can take place in healthcare settings outside those provided for in the REMS. When an approved drug that is subject to a REMS is studied in a clinical trial, the REMS does not apply to the use of the drug in that clinical trial. However, FDA reviews the protocol to ensure that it will be conducted in a manner that adequately addresses the risks that the REMS is intended to mitigate, such that the trial participants will not be exposed to an unreasonable and significant risk of illness or injury. See 21 CFR 312.42(b)(1)(i) and (b)(2)(i).

<sup>81</sup> Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. *Obstet Gynecol* 2021;137:613–22; Rocca CH, Puri M, et al. Effectiveness and safety of early medication



Docket No. FDA-2019-P-1534

and dispensing mifepristone from pharmacies by mail.<sup>82</sup> Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to patients,<sup>83</sup> and (2) prescribers using couriered delivery of medications.<sup>84</sup> Different studies have evaluated dispensing mifepristone by mail by an entity described as “a partner organization.”<sup>85</sup>

We note that the ability to generalize the results of these studies to the United States population is hampered by differences between the studies with regard to pre-abortion care (e.g., telemedicine versus in-person). In addition, the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy. There are also factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation (for example, most studies on mail dispensing of mifepristone also include telemedicine consultation); and (2) because most serious adverse events with medical abortion are infrequent, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States. Despite the limitations of the studies we reviewed, we have concluded that overall the outcomes of these studies are not inconsistent with our conclusion that, based on the 1<sup>st</sup> 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.

---

abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. *PLoS ONE* 13(1): e0191174. <https://doi.org/10.1371/journal.pone.0191174>; Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. *Contracept X*. 2020; 2: 100023.

<sup>82</sup> Grossman D, Raifman S, Morris N, et al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception* 2021, ISSN 0010-7824, <https://doi.org/10.1016/j.contraception.2021.09.008>, Available online 20 September 2021; Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. *JAMA Network Open*. 2021;4(8):e2122320, doi:10.1001/jamanetworkopen.2021.22320; Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. *Aust N Z J Obstet Gynaecol* 2018;58: 335-340.

<sup>83</sup> See Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. *Contraception* 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online. Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. *Contraception* 2019; 100:173-177. See also Chong et al., *infra* n. 103 Kerestes et al., *infra* n. 105, and Aiken et al., *infra* n. 106.

<sup>84</sup> Reynolds-Wright JJ, et al. *BMJ Sex Reprod Health* 2021;0:1–6. doi:10.1136/bmjsex-2020-200976.

<sup>85</sup> Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. *BJOG* 2019;126:609-618. Norton H, Ilozumba O, Wilkinson J, Gemzell Danielsson K, Gomperts R. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. *BJOG* 2021; <https://doi.org/10.1111/1471-0528.16765>; Aiken ARA, Digol I, Trussell J, Gomperts R. Self-reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. *BMJ* 2017;357:j2011 <http://dx.doi.org/10.1136/bmj.j2011>.

Docket No. FDA-2019-P-1534

Below is a summary of our review of the literature, organized by the methods of dispensing mifepristone that were studied.

(a) Retail pharmacy dispensing

Three studies reported medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation (Grossman,<sup>86</sup> Rocca,<sup>87</sup> Wiebe<sup>88</sup>). Grossman conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic. Complete abortion without additional procedures occurred in 93.5 percent of participants with known outcomes. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. No participants experienced a serious adverse event, were hospitalized or required transfusion. Three participants had emergency department (ED) visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study safety and efficacy outcomes are consistent with labeled outcome frequencies. The study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to United States retail pharmacies; there is insufficient information to assess this.

Rocca<sup>89</sup> conducted an observational study evaluating participants who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. The authors reported that, with respect to complete abortion (greater than 97 percent) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,<sup>90</sup> in a retrospective, chart review study conducted in Canada, compared abortion outcomes of women who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (equal to or greater than 95 percent participants with known outcomes). The telemedicine group had one case of hemorrhage (0.5 percent) and one case of infection requiring antibiotics (0.5 percent) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3 percent compared to 1.5 percent in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

---

<sup>86</sup> Grossman et al., supra n. 81.

<sup>87</sup> Rocca et al., supra n. 81.

<sup>88</sup> Wiebe et al., supra n. 81.

<sup>89</sup> Rocca et al., supra n. 81.

<sup>90</sup> Wiebe et al., supra n. 81.

Docket No. FDA-2019-P-1534

None of the three studies allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the results of the studies to the current retail pharmacy environment in the United States. The outcome findings from the one United States study (Grossman)<sup>91</sup>, in which the pharmacies were partnered with prescribers, are unlikely to be broadly generalizable to the current retail pharmacy environment and do not reflect typical prescription medication availability with use of retail pharmacy dispensing. For the retail pharmacy dispensing study in Canada (Wiebe),<sup>92</sup> timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that would allow timely access to medications for medical abortion would occur in retail pharmacies throughout the United States, suggesting the findings from that study may not be broadly generalizable. The third study (Rocca)<sup>93</sup> evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the United States retail setting.

(b) Mail order pharmacy

Three studies evaluated mail order pharmacy dispensing (Grossman,<sup>94</sup> Upadhyay,<sup>95</sup> Hyland<sup>96</sup>). Grossman published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. Complete abortion without additional procedures occurred in 96.9 percent of participants with known outcomes. Two (0.9 percent) participants experienced serious adverse events; one received a blood transfusion and one was hospitalized overnight. Nine (4 percent) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies.

Upadhyay<sup>97</sup> reports findings from a retrospective cohort study of women undergoing medical abortion in the United States without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Abortion outcome was determined by either an assessment on day 3 or a 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95 percent for participants with known outcomes and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. As recommended in Section 2.3 of the approved labeling, follow-up at

---

<sup>91</sup> Grossman et al., supra n. 81.

<sup>92</sup> Wiebe et al., supra n. 81.

<sup>93</sup> Rocca et al., supra n. 81.

<sup>94</sup> Grossman et al, supra n. 82.

<sup>95</sup> Upadhyay et al., supra n. 82.

<sup>96</sup> Hyland et al., supra n. 82.

<sup>97</sup> Upadhyay et al., supra n. 82.



Docket No. FDA-2019-P-1534

7-14 days after administration of mifepristone is more appropriate to evaluate safety and efficacy. This study used a model with numerous deviations from standard provision of medical abortion in the United States, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland<sup>98</sup> describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. Complete abortions without additional procedures occurred in 96 percent of participants with documented outcomes and is consistent with labeled efficacy. Of the participants included in the analysis, 95 percent had no face-to-face clinical encounters after medications were mailed while 3 percent were admitted to the hospital and 2 percent had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have “full follow up.” The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. However, the reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported frequency of hospitalizations (3 percent) is higher than the less than 1 percent in the FDA-approved mifepristone labeling, conclusions on the safety findings cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that efficacy of medical abortion is maintained with mail order pharmacy dispensing. With respect to safety, in the Grossman study<sup>99</sup> the interim analysis, although small, does not raise serious safety concerns. Safety findings from the Hyland<sup>100</sup> study are difficult to interpret. Although only one transfusion is reported and the authors state the findings demonstrate safety, a higher hospitalization rate and lack of information on the reasons for hospitalization preclude reaching any conclusions about the safety findings. Lastly, the Upadhyay<sup>101</sup> study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the United States.

(c) Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail. Gynuity Health Projects conducted a prospective cohort study (the “TelAbortion” study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population exclusively: Raymond (outcomes from May 2016 to December

<sup>98</sup> Hyland et al., supra n. 82.

<sup>99</sup> Grossman et al., supra n. 82.

<sup>100</sup> Upadhyay et al., supra n. 82.

<sup>101</sup> Hyland et al., supra n. 82.

Docket No. FDA-2019-P-1534

2018),<sup>102</sup> Chong (outcomes from May 2016 to September 2020)<sup>103</sup> and Anger (outcomes from March 2020 to September 2020).<sup>104</sup> A fourth study, Kerestes,<sup>105</sup> reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020 and a fifth study, Aiken (2021)<sup>106</sup> reports outcomes of medical abortion up to 70 days gestational age in the United Kingdom before and during the COVID-19 PHE in a retrospective cohort study.

In Raymond,<sup>107</sup> complete abortion without additional procedures occurred in 93 percent of participants with known outcomes. There were two hospitalizations (one participant received a transfusion for severe anemia despite having had a complete abortion) and 7 percent of participants had clinical encounters in ED/urgent care centers. The reported outcomes are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).<sup>108</sup> Of note, the authors state that half of the ED/urgent care visits did not entail any medical treatment. In Chong,<sup>109</sup> approximately 50 percent of the medical abortions occurred during the period of the COVID-19 PHE. Complete abortion without an additional procedure occurred in 95 percent of those with known outcomes. Transfusions were 0.4 percent and hospitalizations were 0.7 percent; 6 percent of participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 4.1 percent to complete abortion. The reported outcomes in Chong (which updated the findings described in Raymond) are similar to outcomes described in approved labeling except that (as with the Raymond study it updated) the combined ED/urgent care center encounters (6 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).

Anger,<sup>110</sup> which compared outcomes among participants enrolled in the Gynuity study who did (“test medical abortion cohort”) versus did not (“no-test medical abortion cohort”)<sup>111</sup>

<sup>102</sup> Raymond et al., supra n. 83.

<sup>103</sup> Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. *Contraception* 2021;104:43-48.

<sup>104</sup> Anger et al., supra n. 83.

<sup>105</sup> Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. *Contraception* 2021 Jul;104(1):49-53. doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.

<sup>106</sup> Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. *BJOG* 2021;128:1464-1474.

<sup>107</sup> Raymond, supra n. 83.

<sup>108</sup> The authors reported the combined frequency of emergency department/urgent care visits, whereas the approved labeling includes the frequency for emergency department (emergency room) visits. Therefore it is unknown whether the frequency of emergency department visits in the trial, as distinct from the combined frequency of emergency department/urgent care visits, is comparable to the frequency of emergency department visits reflected in approved labeling.

<sup>109</sup> Chong et al., supra n. 103.

<sup>110</sup> Anger et al., supra n. 83.

<sup>111</sup> “No-test medication abortion” refers to medical abortion provided without a pretreatment ultrasound, pelvic examination or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); “no-test medication abortion” does include post-abortion follow up. A sample protocol is described by Raymond et al.” (Raymond EG, Grossman D, Mark A, et al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. *Contraception* 2020;101:361-366)

Docket No. FDA-2019-P-1534

have confirmation of gestational age/intrauterine location with an examination or ultrasound, found that those without an examination or ultrasound prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.<sup>112</sup> There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the “test” group, complete medical abortion was confirmed in 98 percent of participants with known outcomes; one participant was “hospitalized and/or blood transfusion” and 8 percent had an unplanned clinic encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion). In the “no-test” group, complete medical abortion was confirmed in 94 percent of participants with known outcomes; two participants were “hospitalized and/or blood transfusion” and 12.5 percent had an unplanned clinical encounter.

Kerestes<sup>113</sup> included three different delivery models: traditional in-person visits, telemedicine consultation with in-person pick-up of medications, and telemedicine consultation with delivery of medications by mail (most of the latter were enrolled through Gynuity’s TelAbortion study). Among participants with follow-up data, the rates of successful medical abortion without surgery were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine plus in-person pickup group). Although ED visits occurred the most frequently in the telemedicine plus mail group (four participants or 5.8 percent) and the least in the in-person group (two participants or 2.1 percent), the study reported no increases in other serious adverse events. Aiken (2021)<sup>114</sup> reported outcomes before and during the pandemic in a retrospective cohort study in the United Kingdom. The study compared the two cohorts: one before the pandemic with in-person visits and dispensing (traditional model) and one during the pandemic with either an in-person visit and in-person dispensing or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Complete abortion occurred in greater than 98 percent in both cohorts; the rate was slightly higher in the telemedicine group than in the in-person group. There were no significant differences in the rates of reported serious adverse events. The investigators’ analysis determined that the efficacy and safety were comparable between both cohorts and concluded the hybrid model for medical abortion is effective and safe.

Taken together, data from the three Gynuity study reports (Raymond, Chong, and Anger), Kerestes, and Aiken (2021) support that efficacy of medical abortion was maintained when mifepristone was dispensed by mail from the clinic. Study reports of Raymond, Chong, and Kerestes all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail from the clinic, but without increases in other serious adverse events. Anger’s comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. The Aiken (2021) study appears to be of sufficient

---

<sup>112</sup> We note that the two cohorts were not randomized in the Anger study; they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

<sup>113</sup> Kerestes et al., *supra* n. 105.

<sup>114</sup> Aiken et al., *supra* n. 106.



Docket No. FDA-2019-P-1534

sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, significant limitations include that the analysis was based on deidentified information and the investigators were unable to verify the outcomes extracted. Further, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

Notwithstanding the limitations discussed above, these studies overall support that dispensing by mail from the clinic is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use.

(d) Clinic dispensing by courier

Reynolds-Wright<sup>115</sup> reported findings from a prospective cohort study of participants at less than 12 weeks gestational age in Scotland undergoing medical abortion at home that provided mifepristone for pick up at the service or by couriered delivery to woman's home. The outcomes from this study in Scotland are consistent with the outcomes in the approved mifepristone labeling. However, the number of couriered deliveries was not reported. Thus this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. The study shares the same limitations as the Aiken (2021) study; the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

(e) Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail. WoW uses a model with numerous deviations from the standard provision of medical abortion in the United States. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Three studies (Endler, Nortén, and Aiken (2017))<sup>116</sup> reported outcomes based on dispensing through this model. Endler and Nortén reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail because neither provide meaningful outcomes data for consideration. Although Aiken (2017) is a large cohort study, the outcomes are self-reported and an unusually high rate of outcomes are unaccounted for; these limitations result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

In sum, there are insufficient data from the literature we have reviewed to determine the safety and efficacy of dispensing from a retail pharmacy, by courier, or by a partner organization. With respect to dispensing mifepristone by mail, our review of the literature indicates that dispensing mifepristone by mail from the clinic or from a mail order

<sup>115</sup> Reynolds-Wright JJ, et al. *BMJ Sex Reprod Health* 2021;0:1–6. doi:10.1136/bmjsex-2020-200976.

<sup>116</sup> Endler et al., Nortén et al., and Aiken et al., supra n. 85.

Docket No. FDA-2019-P-1534

pharmacy does not appear to jeopardize the efficacy of mifepristone for medical abortion. While the studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, the safety and efficacy outcomes reported in these studies remain within the ranges labeled for the approved mifepristone products. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other significant adverse events related to mifepristone use.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, and our review of the literature, we conclude that mifepristone will remain safe and effective if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added. Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the Mifepristone REMS Program, the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

In your Petition, you state that “[e]liminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls” and that “health care providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs” (Petition at 18-19).

We do not agree that eliminating the REMS requirement for the dispensing of Mifeprex in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of healthcare providers to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. There are many factors that contribute to patient safety, including evaluation of a patient, informed consent, development of a follow-up plan, and provision of a contact for emergency care. All of these can occur in many types of healthcare settings. The evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber.

You also assert that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19). We do not agree. Healthcare providers who prescribe mifepristone are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the American Medical Association that a healthcare provider-patient relationship is entered when the “physician serves a patient’s medical needs;”<sup>117</sup> in the context of medical abortion, this

---

<sup>117</sup> See [www.ama-assn.org/delivering-care/ethics/patient-physician-relationships](http://www.ama-assn.org/delivering-care/ethics/patient-physician-relationships).

Docket No. FDA-2019-P-1534

healthcare provider-patient relationship continues until resolution of the pregnancy or transfer of care to another healthcare provider.<sup>118</sup>

We also note that patients who are not pregnant at the time of evaluation would not be appropriate candidates for being prescribed mifepristone for medical termination of pregnancy because they do not fulfill the approved indication of having an intrauterine pregnancy of up to 70 days gestation.

## 2. Other Safety Issues and Additional Studies

In support of your request that we retain the Mifeprex REMS, you cite the Council for International Organizations of Medical Sciences' (CIOMS) definition of "rare" to assert that because "about 1 out of 100 women" using Mifeprex and misoprostol require surgery, serious complications are common, not rare (Petition at 15-16).<sup>119</sup> Although we agree that certain elements of the Mifepristone REMS Program are necessary to assure the safe use of mifepristone, we do not agree with your assertion.

In the Petition, you state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and you cite the Medication Guide as stating "*rarely*, serious and potentially life-threatening bleeding, infections, and other problems can occur following . . . medical abortion." Specifically, "in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure." (Petition at 15). Using these two separate statements in the Medication Guide, you argue that the CIOMS's definition of rare ("1 out of 1000") means that if 1 out of 100 women using Mifeprex in a regimen with misoprostol require surgery, serious complications are common, not rare. (Petition at 16). However, your reference to the two sentences in the Medication Guide conflates two different clinical scenarios: (1) the adverse event of serious and potentially life-threatening bleeding, and (2) treatment failure.

The first sentence you reference states: "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." This statement refers to life-threatening adverse events that can occur during termination regardless of gestational age or during miscarriage or childbirth regardless of the mode of delivery (e.g., vaginal delivery or cesarean section). At the time of our review of the clinical studies submitted to support the S-020 efficacy supplement, the reported rate of death in the studies reviewed, based on one death, was 0.007 percent (very rare under the CIOMS definition).<sup>120</sup> The rate of infections requiring hospitalization or

<sup>118</sup> See <https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine>.

<sup>119</sup> Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition. 1999. <https://cioms.ch/wp-content/uploads/2018/03/Guidelines-for-Preparing-Core-Clinical-Safety-Info-Drugs-Report-of-CIOMS-Working-Group-III-and-V.pdf>. Accessed December 13, 2021 (CIOMS).

<sup>120</sup> Id. at 36 (defining the "very rare" standard category of frequency as less than 0.01 percent).



Docket No. FDA-2019-P-1534

intravenous antibiotics was less than 0.1 percent (rare under the CIOMS definition),<sup>121</sup> and rates of transfusion were 0.03-0.7 percent (rare to uncommon under the CIOMS definition).<sup>122</sup> Therefore, “rarely” accurately refers to the frequency of the adverse events referenced in this statement.

The second sentence you reference from the Medication Guide states: “In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).” This statement refers to the rate of surgical procedures for bleeding following treatment with mifepristone. Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the CIOMS definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion. Furthermore, in the vast majority of medical abortions, surgical intervention is not necessary.

You also cite a 2009 study and a 2018 study to assert that medical abortions carry greater risks than surgical abortions (Petition at 16). The 2009 Niinimaki, et al.<sup>123</sup> study reported overall incidences of immediate adverse events (up to 42 days) in medical and surgical abortions performed in women undergoing induced abortion from 2000-2006 based on data from the Finnish national registries. We agree that the overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0 percent versus 5.6 percent). Specifically, the incidence of hemorrhage, incomplete abortion, and surgical (re)evacuation were higher for medical abortion. However, the authors specifically noted that because medical abortion is associated with longer uterine bleeding, the high rate of events, which were pulled from a national registry reflecting both inpatient and outpatient visits, is not surprising. They opined that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy; the incidence of such bleeding was relatively low, although it was more common with medical abortion. In addition, the authors acknowledged there are inherent weaknesses in registry-based studies; there is variable reliability both of diagnoses and of severity of diagnoses. Nevertheless, the authors concluded that both methods are generally safe and recommended discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination.

We note that Ireland, et al.<sup>124</sup> reported findings from a more recent retrospective cohort study of 30,146 United States women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6 percent and 99.8 percent for medical and surgical abortion, respectively.

<sup>121</sup> Id. at 36 (defining the “rare” standard category of frequency as greater than or equal to 0.01 percent and less than 0.1 percent).

<sup>122</sup> Id. at 36 (defining the “uncommon” standard category of frequency as greater than or equal to 0.1 percent and less than 1 percent); see also 2016 Clinical Review, supra n. 13, at 47 and 51.

<sup>123</sup> Niinimaki M, Pouta A, Bloigu A, et al. Immediate complications after medical compared with surgical termination of pregnancy. *Obstet Gynecol.* 2009;114(4):795-804.

<sup>124</sup> Ireland LD, Gatter, M, Chen, A. 2015. Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the First Trimester. *Obstetrics & Gynecology* 126:22-28.

Docket No. FDA-2019-P-1534

Unanticipated aspiration for persistent pain, bleeding or both were 1.8 percent and 0.4 percent for medical and surgical abortion respectively. These findings are compatible with the Niinimaki study findings. There was no difference in major adverse events as defined by the authors (emergency department visit, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion) between the groups. The authors conclude medical and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

The 2018 Carlsson study is addressed above in section II.A.2.b.ii. of this response; as discussed above, that study showed no statistically significant difference between the overall complication rates between an “at home” and “at the hospital” abortion.<sup>125</sup>

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical abortion. However, as noted above, in the vast majority of medical abortions, surgical intervention is not necessary. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. Patients and their healthcare providers should discuss which method is preferable and safer according to each woman’s unique situation.

You state that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13-14). As we explain below, additional studies are not needed at this time.

In justifying your assertion that a formal study is required in patients under the age of 18, you state that Mifeprex was approved for use in the pediatric population in 2000 after the requirement for studies in the pediatric population was waived (Petition at 13-14). The approved indication for mifepristone does not limit its use by age. Although patients age 17 and under were not included in the clinical trials supporting the initial approval of Mifeprex in 2000, we stated at the time that the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents. Our conclusion in 2000 that pediatric studies of Mifeprex were not needed for approval was consistent with FDA’s implementation of the regulations in effect at that time. Because we determined that there were sufficient data from studies of mifepristone, the original Mifeprex approval should have reflected the Agency’s conclusion that the pediatric study requirements were waived for pre-menarchal females and that the pediatric study requirements were met for post-menarchal adolescents, rather than stating that the Agency was waiving the requirements for all pediatric age groups.

As currently required by the Pediatric Research Equity Act (PREA),<sup>126</sup> certain applications or supplemental applications must include pediatric assessments of the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric

---

<sup>125</sup> Carlsson et al., *supra* n. 49.

<sup>126</sup> Section 505B of the FD&C Act (21 U.S.C. 355c).

Docket No. FDA-2019-P-1534

subpopulations, unless that requirement is waived or deferred.<sup>127</sup> In accordance with PREA, when FDA reviewed the S-020 efficacy supplement, a partial waiver was granted for pediatric studies in pre-menarchal females because pregnancy does not occur in premenarchal females. We also determined that the applicant had fulfilled the pediatric study requirement in post-menarchal adolescents. This determination was based on data extrapolated from adults and information in literature. Review of these findings found the safety and efficacy in this population to be similar to the safety and efficacy in the adult population.<sup>128</sup> Therefore, we do not agree that a formal study is required in patients under 18.

With regard to your concerns about repeat abortions and your assertion that a study is necessary in this population, we acknowledge that published data concerning adverse reproductive health outcomes in U.S. women who undergo repeat medical abortions are limited. We concluded in our 2016 review of the S-020 efficacy supplement that there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. We also noted that return to fertility after the use of mifepristone is well documented.<sup>129</sup> This is reflected both in Section 17 of the approved labeling, Patient Counseling Information, which states that the provider should “inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses,” and in the Medication Guide, which states “You can become pregnant again right after your pregnancy ends.” Although you state that more than one out of every three abortions in the United States is a repeat abortion (Petition at 14),<sup>130</sup> we are not aware of reports suggesting greater safety concerns in repeat abortions than a first-time abortion. Therefore, we do not agree that a study is necessary in this population. You also cite a published study, using a mouse model, of repeated medical termination of pregnancy that showed repeat medical abortion impaired the reproductive function of female mice (Petition at 14).<sup>131</sup> Per our 2016 review, there is no evidence in available clinical data that repeated medical or surgical abortion is unsafe, or that fertility is impaired by the use of mifepristone; therefore, data from a single non-clinical study in mice are not persuasive.<sup>132</sup>

With respect to your request for a formal study of mifepristone for medical abortion in women without access to emergency care, we disagree that such a study is necessary. In order to become a certified prescriber, a healthcare provider must agree that they have the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others, and that they have the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. These prescriber qualifications ensure that mifepristone is prescribed to women for whom emergency care is available.

<sup>127</sup> Section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2)).

<sup>128</sup> 2016 Clinical Review, *supra* n. 13, at 74-76.

<sup>129</sup> *Id.* at 47.

<sup>130</sup> In support of this assertion, you cite Jones R, Jerman J, Ingerick M. Which abortion patients have had a prior abortion? Findings from the 2014 U.S. Abortion Patient Survey. *J Womens Health*.

<sup>131</sup> Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. *PLoS One*. 2012;7(10):e48384. doi:10.1371/journal.pone.0048384.

<sup>132</sup> 2016 Clinical Review, *supra* n. 13, at 47.



Docket No. FDA-2019-P-1534

Finally, you assert that FDA should require a formal study in patients who self-administer misoprostol. As explained in section II.A.2.b.ii of this response, FDA conducted a literature review of self-administration of misoprostol at home as part of its review of the S-020 efficacy supplement and found no safety or efficacy concerns with home self-administration of misoprostol. Therefore, we disagree that a formal study is required in this population.

With regard to safety generally, in addition to the FAERS data provided above (see section II.B.1.c.ii. in this response), FDA routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy through 70 days gestation. We have not identified any new safety concerns with the use of mifepristone for this indication.

### 3. Other Articles

In your Petition, you reference several documents that discuss alternative models of providing abortion medications and advocate for the lifting of the REMS on mifepristone (Petition at 23-24). You assert that these recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex.<sup>133</sup>


We agree that the overarching message in the publications you reference appears to be advocating self-management of medical abortion. Nonetheless, as discussed in this response, we have determined that the Mifepristone REMS Program continues to be necessary for the safe use of this drug product, with some modifications.

### III. CONCLUSION

For the reasons set forth above, we deny your request that FDA restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000; and we grant in part and deny in part your request to retain the Mifepristone REMS Program. As with all approved drug products, we will continue to monitor the safety of mifepristone for the approved indication and take any appropriate actions.

Sincerely,

Patrizia A.  
Cavazzoni -S

 Digitally signed by Patrizia A.  
Cavazzoni -S  
Date: 2021.12.16 15:05:41 -05'00'

Patrizia Cavazzoni, M.D.  
Director  
Center for Drug Evaluation and Research

---

<sup>133</sup> You also reference clinical trials relating to the use of mifepristone for spontaneous miscarriage management and question the results of studies related to this use (Petition at 16-18). The use of mifepristone for the management of early miscarriage is not an approved indication for this drug product and is outside the scope of the Mifepristone REMS Program. Therefore, we do not address it in this response.

# Exhibit 44

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

## Questions and Answers on FDA's Adverse Event Reporting System (FAERS)

### What is FAERS?

The FDA Adverse Event Reporting System (FAERS) is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation ([ICH E2B \(/drugs/guidances-drugs/international-council-harmonisation-efficacy\)](http://www.ich.org)). Adverse events and medication errors are coded using terms in the [Medical Dictionary for Regulatory Activities \(MedDRA\) \(http://www.meddra.org/\)](http://www.meddra.org/) [↗ \(http://www.fda.gov/about-fda/website-policies/website-disclaimer\)](http://www.fda.gov/about-fda/website-policies/website-disclaimer) terminology.

### How does FDA use the information in FAERS?

FAERS is a useful tool for FDA for activities such as looking for new safety concerns that might be related to a marketed product, evaluating a manufacturer's compliance to reporting regulations and responding to outside requests for information. The reports in FAERS are evaluated by clinical reviewers, in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), to monitor the safety of products after they are approved by FDA.

If a potential safety concern is identified in FAERS, further evaluation is performed. Further evaluation might include conducting studies using other large databases, such as those available in the [Sentinel System \(/sentinel-initiative-transforming-how-we-monitor-product-safety\)](http://www.fda.gov/oc/initiatives/sentinel). Based on an evaluation of the potential safety concern, FDA may take regulatory action(s) to improve product safety and protect the public health, such as updating a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market.

### Who sends reports to FAERS?

Healthcare professionals, consumers, and manufacturers submit reports to FAERS. FDA receives voluntary reports directly from healthcare professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others). Healthcare professionals and consumers may also report to the products' manufacturers. If a manufacturer receives a report from a healthcare professional or consumer, it is required to send the report to FDA as specified by regulations.

### How can I report an adverse event or medication error to FDA?

The [MedWatch \(https://www.fda.gov/Safety/MedWatch/default.htm\)](https://www.fda.gov/Safety/MedWatch/default.htm) website provides information about [voluntary and mandatory reporting \(https://www.fda.gov/Safety/MedWatch/HowToReport/default.htm\)](https://www.fda.gov/Safety/MedWatch/HowToReport/default.htm).

### Can mandatory reporters submit adverse events electronically?

Yes, the [FDA Adverse Events Reporting System \(FAERS\) Electronic Submissions \(/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions\)](http://www.fda.gov/drugs/surveillance/faq-fda-adverse-event-reporting-system-faers) website provides drug and therapeutic biological product manufacturers, distributors, packers, and other interested parties with information about FDA Adverse Event Reporting System (FAERS) electronic submissions and instructions on how to electronically submit post-marketing individual case safety reports (ICSRs), with and without attachments.



## Does FAERS data have limitations?

Yes, FAERS data does have limitations. First, there is no certainty that the reported event (adverse event or medication error) was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Furthermore, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. There are also duplicate reports where the same report was submitted by a consumer and by the sponsor. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population. For more information, please refer to the question “[What points should I consider while viewing the dashboard content? \(https://fis.fda.gov/extensions/fpdwidgets/2e01da82-13fe-40e0-8c38-4da505737e36.html#\\_Toc493751926\)](https://fis.fda.gov/extensions/fpdwidgets/2e01da82-13fe-40e0-8c38-4da505737e36.html#_Toc493751926)”

## Is FAERS data available to the public?

FAERS data is available to the public in the following ways:

- [FAERS dashboard \(/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard\)](/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard): a highly interactive web-based tool that allows for the querying of FAERS data in a user friendly fashion.
- [FAERS data files \(/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files\)](/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files): provides raw data consisting of individual case safety reports extracted from the FAERS database. A simple search of FAERS data cannot be performed with these files by persons who are not familiar with the creation of relational databases.
- Individual case safety reports from the FAERS database can also be obtained by sending a [Freedom of Information \(FOI\) request to FDA \(/how-make-foia-request\)](/how-make-foia-request).

## How do I find or confirm my report is in FAERS?

To confirm that your report is in FAERS, please send a [Freedom of Information \(FOI\) request to FDA \(/how-make-foia-request\)](/how-make-foia-request).

## What are the benefits of the FAERS public dashboard?

This tool makes the data easier to query and produces user-friendly information and charts. For example, users can view a summary of adverse event reports received from 1968 to the present or for a specific timeframe. In addition, users can search on a product of interest within a specific timeframe.

## Will there be a tutorial so I can learn how to use this database?

Yes, a [recorded webinar \(/about-fda/pharmacy-student-experiential-program/fda-drug-topics-fda-adverse-events-reporting-system-faers-public-dashboard-january-30-2018\)](/about-fda/pharmacy-student-experiential-program/fda-drug-topics-fda-adverse-events-reporting-system-faers-public-dashboard-january-30-2018) is available which reviews the capabilities, and limitations, of the FAERS public dashboard.

## Is the FAERS public dashboard accessible on an Android™ or iPhone®?

Yes, but the user interface layout may not be very user friendly. FDA will continue to work on the dashboard to make the user interface Android and iPhone friendly.

## Can I download my search results from the dashboard?

11/9/22, 1:59 PM

Questions and Answers on FDA's Adverse Event Reporting System (FAERS) | FDA

Yes, you will be able to export a limited set of search data to an Excel® spreadsheet and then download it. FDA will still continue to provide the [FAERS Latest Quarterly Data Files \(/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files\)](https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files) online.

Note: The data fields listed on the FAERS Dashboard currently is a subset of the data fields available in the FAERS Quarterly Data files. Future release of the FAERS Dashboard plans to make the other data fields available. Also the data displayed in the FAERS Dashboard may not be identical to the data in the FAERS Quarterly Data files due to different data extraction dates.

## Where else can I find safety information?

- [Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System \(FAERS\): quarterly reports on potential serious side effects identified by FAERS. \(/drugs/fda-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system\)](https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system)
- [Post-marketing Drug and Biologic Safety Evaluations \(/drugs/surveillance/postmarket-drug-and-biologic-safety-evaluations\)](https://www.fda.gov/drugs/surveillance/postmarket-drug-and-biologic-safety-evaluations): provides summary information about ongoing and completed post-marketing safety evaluations of adverse experience reports made to FDA for New Drug Applications (NDAs) and Biologic License Applications (BLAs) approved since September 27, 2007.
- Center for Drug Evaluation and Research (CDER): [Drug Safety and Availability \(https://www.fda.gov/Drugs/DrugSafety/default.htm\)](https://www.fda.gov/Drugs/DrugSafety/default.htm)
- [Post-market Drug Safety Information for Patients and Providers \(https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm\)](https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm)
- [MedWatch: The FDA Safety Information and Adverse Event Reporting Program \(https://www.fda.gov/Safety/MedWatch/default.htm\)](https://www.fda.gov/Safety/MedWatch/default.htm)

## How are versions of a case in FAERS handled?

Each unique submission of a case received is assigned a version number (for example, Case #1234567, version 1). The initial version received will be version 1. If a follow up is received on a previously submitted case, then that version of the case will be version 2, and so on. The latest version of a case represents the most current information about that case.

The data is updated quarterly.

## What points should I consider while viewing the dashboard content?

When you view the website output of reported reactions (side effects or adverse drug reactions) for a drug product, it is important to consider the following points:

- **Data Quality:** There are many instances of duplicative reports and some reports do not contain all the necessary information. Duplicate reporting occurs when the same report is submitted by the consumer and the sponsor. The information in FAERS evolves daily and the number of individual cases may increase or decrease. It is therefore possible that the information on this website may change over time.
- **Existence of a report does not establish causation:** For any given report, there is no certainty that a suspected drug caused the reaction. While consumers and healthcare professionals are encouraged to report adverse events, the reaction may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.

11/9/22, 1:59 PM

Questions and Answers on FDA's Adverse Event Reporting System (FAERS) | FDA

- **Information in reports has not been verified:** Submission of a report does not mean that the information included in it has been medically confirmed nor it is an admission from the reporter that the drug caused or contributed the event.
- **Rates of occurrence cannot be established with reports:** The number of suspected reactions in FAERS should not be used to determine the likelihood of a side effect occurring. The FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, information in these reports cannot be used to estimate the incidence (occurrence rates) of the reactions reported.
- **Patients should talk to their doctor** before stopping or changing how they take their medications.
- **Patient Outcomes received in FAERS:** These data describe the outcome of the patient as defined in U.S. reporting regulations (21 CFR 310.305, 314.80, 314.98, 600.80). Serious means that one or more of the following outcomes were documented in the report: death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome. Documenting one or more of these outcomes in a report does not necessarily mean that the suspect product(s) named in the report was the cause of the outcomes.

Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug.



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**020687Orig1s020**

**MEDICAL REVIEW(S)**

Clinical Review:

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

## CLINICAL REVIEW

Application Type	SE-2 Efficacy Supplement
Application Number(s)	NDA 020687/S-020
Priority or Standard	Standard
Submit Date(s)	May 28, 2015
Received Date(s)	May 29, 2015
PDUFA Goal Date	March 29, 2016
Division / Office	(b) (6)
Reviewer Name(s)	(b) (6) and (b) (6)
Review Completion Date	March 29, 2016
Established Name	Mifepristone
(Proposed) Trade Name	Mifeprax
Therapeutic Class	Progestin antagonist
Applicant	Danco Laboratories, LLC
Formulation(s)	Oral Tablet
Dosing Regimen	For pregnancies through 70 days gestation: Mifeprax 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol.
Indication(s)	Mifeprax is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.
Intended Population(s)	Pregnant women who desire a medical termination through 70 days gestation.

Clinical Review:

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT</b>	<b>5</b>
1.1	Recommendation on Regulatory Action	5
1.2	Risk Benefit Assessment	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies	7
1.4	Recommendations for Postmarket Requirements and Commitments	8
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND</b>	<b>9</b>
2.1	Product Regulatory Information	9
2.2	Tables of Currently Available Treatments for Proposed Indications	9
2.3	Availability of Proposed Active Ingredient in the United States	10
2.4	Important Safety Issues with Consideration to Related Drugs	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission	11
2.6	Other Relevant Background Information	11
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES</b>	<b>13</b>
3.1	Submission Quality and Integrity	13
3.2	Compliance with Good Clinical Practices	13
3.3	Financial Disclosures	13
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES</b>	<b>14</b>
4.1	Chemistry Manufacturing and Controls (CMC)	14
4.2	Clinical Microbiology	14
4.3	Preclinical Pharmacology/Toxicology	14
4.4	Clinical Pharmacology	15
4.4.1	Mechanism of Action	15
4.4.2	Pharmacodynamics	15
4.4.3	Pharmacokinetics	15
<b>5</b>	<b>SOURCES OF CLINICAL DATA</b>	<b>17</b>
5.1	Tables of Studies/Clinical Trials	17
5.1.1	Submissions during the Review Process	19
5.2	Review Strategy	20
5.2.1	Discussion of Individual Studies/Clinical Trials	21
<b>6</b>	<b>REVIEW OF EFFICACY</b>	<b>21</b>
	Efficacy Summary	21
6.1	Indication	22
6.1.1	Methods	23
6.1.2	Demographics	23
6.1.3	Subject Disposition	23
6.1.4	Analysis of Primary Endpoint(s)	23



## Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

6.1.5	Analysis of Secondary Endpoints(s).....	24
6.1.6	Proposal for a New Dosing Regimen .....	24
6.1.7	Increase in gestational age from 49 days to 70 days .....	32
6.1.8	At-home Administration of Misoprostol.....	38
6.1.9	Use of a Repeat Dose of Misoprostol if Needed .....	41
6.1.10	Physician v Other Healthcare Provider Treatment .....	43
6.1.11	Follow-up Timing and Method.....	44
6.1.12	Subpopulations .....	44
6.1.13	Analysis of Clinical Information Relevant to Dosing Recommendations ...	46
6.1.14	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	47
6.1.15	Additional Efficacy Issues/Analyses .....	47
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>47</b>
	Safety Summary .....	47
7.1	Methods.....	49
7.1.1	Studies/Clinical Trials Used to Evaluate Safety .....	49
7.1.2	Categorization of Adverse Events.....	50
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	50
7.2	Adequacy of Safety Assessments.....	50
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	50
7.2.2	Explorations for Dose Response.....	51
7.2.3	Special Animal and/or In Vitro Testing .....	51
7.2.4	Routine Clinical Testing .....	51
7.2.5	Metabolic, Clearance, and Interaction Workup .....	51
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	51
7.3	Major Safety Results .....	51
7.3.1	Deaths.....	51
7.3.2	Nonfatal Serious Adverse Events .....	51
7.3.3	Dropouts and/or Discontinuations .....	57
7.4	Significant Adverse Events.....	57
7.4.1	Submission-Specific Primary Safety Concerns .....	60
7.5	Supportive Safety Results .....	67
7.5.1	Common Adverse Events .....	67
7.5.2	Laboratory Findings .....	71
7.5.3	Vital Signs.....	71
7.5.4	Electrocardiograms (ECGs) .....	71
7.5.5	Special Safety Studies/Clinical Trials.....	71
7.5.6	Immunogenicity.....	71
7.6	Other Safety Explorations.....	71
7.6.1	Additional Safety Evaluations.....	72
7.6.2	Human Carcinogenicity .....	72
7.6.3	Human Reproduction and Pregnancy Data.....	72
7.6.4	Pediatrics and Assessment of Effects on Growth .....	74

Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprax

7.6.5 Overdose, Drug Abuse Potential, Withdrawal and Rebound..... 76  
 7.7 Additional Submissions / Issues ..... 76  
**8 POSTMARKET EXPERIENCE..... 82**  
**9 APPENDICES ..... 85**  
 9.1 Literature Review/References ..... 85  
 9.2 Labeling Recommendations ..... 86  
 9.3 Advisory Committee Meeting..... 86  
 9.4 (b) (6) Meeting ..... 86  
 9.4 Abbreviations..... 90  
 9.5 List of References..... 91  
 9.6 Mifepristone Approvals Globally ..... 99

**Table of Tables**

Table 1: List of Major Studies Reviewed ..... 18  
 Table 2 Clinical Submissions during the Course of the Review ..... 20  
 Table 3: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours  
 Later - US Studies..... 29  
 Table 4: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours  
 Later- Non- US Studies..... 30  
 Table 5: Original NDA Efficacy Results ..... 32  
 Table 6: MAB Efficacy Outcome 57-63 Days Gestation ..... 35  
 Table 7: MAB Efficacy Outcome 64-70 Days Gestation ..... 37  
 Table 8: Misoprostol Self-administration at Home ..... 40  
 Table 9: Success with a Repeat Dose of Misoprostol - Incomplete MAB ..... 42  
 Table 10: MAB Success by Age Group ..... 46  
 Table 11: Studies Used to Evaluate Safety ..... 50  
 Table 12: Hospitalizations by Gestational Age ..... 53  
 Table 13: Serious Infection by Gestational Age ..... 54  
 Table 14: Transfusion by Gestational Age ..... 55  
 Table 15: Uterine Rupture with Misoprostol Case Reports..... 59  
 Table 16: Bleeding and Cramping in Literature ..... 68  
 Table 17: Common Adverse Events in Literature ..... 70  
 Table 18: Age of Adolescents Undergoing Medical Abortion ..... 74  
 Table 19: Serious Adverse Events in Adolescents vs. Adults ..... 74  
 Table 20: Adherence to Follow-Up Among Adolescents vs. Adults..... 76  
 Table 21: US Postmarketing AEs- Mifepristone for Medical Abortion ..... 83  
 Table 22: US Postmarketing Ectopic Cases- Mifepristone for Medical Abortion ..... 84

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

## 1 Recommendations/Risk Benefit Assessment

This NDA supplement from the Applicant, Danco Laboratories, LLC (called Danco or the Applicant throughout this clinical review), requested the following changes to the NDA for Mifeprex, approved 15 years ago in September 2000.

Changes proposed by the Applicant:

1. Change the dosing regimen: Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally
2. Remove the statement in labeling that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman.
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up needed, but not restricted to in-clinic at 14 days after Mifeprex
5. Increase the gestational age from 49 days to 70 days
6. Change the labeled time for expulsion of the products of conception from 4-24 hours to 2-24 hours post misoprostol administration
7. Add that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change "physician" to "(b) (4)" in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change indication to add reference to use of misoprostol: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation."
10. Remove references to "under Federal law" from the Prescriber's Agreement
11. Address the Pediatric Research Equity Act (PREA) requirement for pediatric studies

Each of these 11 items will be discussed in the appropriate section of this review, generally under Section 6: Review of Efficacy and Section 7: Review of Safety. Four of the items, namely Number 8-11, are primarily regulatory and/or legal. They are discussed in Sections 1.3 and 9.4 (REMS recommendations and Prescriber's Agreement), 7.6.4 (PREA), and 9.2 (Labeling recommendation). Additional information is found in Section 7.7 (2) on the change to "(b) (4)" Section 7.7 (3) on "under Federal law", and Section 7.7 (4) on the reference to use of misoprostol.

### 1.1 Recommendation on Regulatory Action

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



Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

## 1.2 Risk Benefit Assessment

1. Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally.

The Applicant has submitted sufficient evidence from the published medical literature to demonstrate that decreasing the dose of Mifeprax from 600 mg to 200 mg while increasing the dose of misoprostol from 400 to 800 mcg is safe and efficacious for termination of pregnancy through 70 days gestation. The risk/benefit balance favors approval.

There is sufficient evidence that a dosing regimen with buccal administration of 800 mcg misoprostol is safe and effective. This change in the dosing regimen should be approved.

2. Allow administration of misoprostol outside of the clinic:

Based on the evidence submitted by the Applicant, a dosing regimen that includes administration of misoprostol outside of the clinic is safe and effective for termination of pregnancy through 70 days gestation; labeling should be revised to remove the requirement for in-clinic dosing of misoprostol

3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprax:

The available evidence supports that a dosing regimen that provides for administration of misoprostol 24-48 hours after administration of Mifeprax is safe and effective. The risk/benefit assessment demonstrates that this change in the dosing regimen should be approved.

4. Follow-up needed, but not restricted to in-clinic at 14 days after Mifeprax:

Based on the evidence submitted by the Applicant supporting this change, flexibility in timing and method of follow-up after medical abortion is safe. Labeling should be revised to remove the requirement for in-clinic follow-up at 14 days.

5. Increase the gestational age from 49 days to 70 days:

As detailed in the following review, the Applicant has submitted sufficient evidence for the safety and efficacy of medical abortion with Mifeprax, in a regimen with misoprostol, through 70 days gestation. The risk/benefit assessment supports the approval of the new dosing regimen up through 70 days gestation.

6. Change the labeled time for expulsion of the products of conception from 4-24 hours to 2-24 hours post misoprostol administration:

The Applicant has submitted sufficient data from the published medical literature to support approval of a change in the label to note time to expulsion ranges from 2-24 hours.

7. Add that a repeat 800 mcg buccal dose of misoprostol may be used if needed:

## Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

The Applicant has submitted sufficient evidence to support that a repeat dose of misoprostol may be used through 70 days gestation to complete expulsion of the products of conception if needed. The risk/benefit assessment supports approval of this change. There have been rare reports of uterine rupture with use of misoprostol in women with prior uterine scar(s). This information should be added to the Mifeprex label.

8. Change “physician” to “(b) (4)” in the labeling and Risk Evaluation and Mitigation Strategies (REMS) document:

The Applicant has submitted sufficient data to support that Mifeprex is safe and effective when prescribed by midlevel practitioners as well as by physicians. Therefore, the term “licensed physician” was changed in the label and REMS materials to “healthcare provider who prescribes.” This broader category of providers will still have to meet the certification criteria specified in the Prescriber Agreement Form.

9. Change the approved indication to add reference to use of misoprostol: “Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.” Based on current Agency labeling practice regarding drugs used together in a treatment regimen, the addition of misoprostol to the Indication Statement for Mifeprex should be approved.

10. Remove references to “under Federal law” from the Prescriber Agreement:

The Agency has determined that there is no precedent for using this phrase in other REMS, nor is there any clinical rationale for including it; therefore, it is acceptable to remove “under Federal law” from the Prescriber Agreement Form.

11. Address the Pediatric Research Equity Act (PREA) requirement for pediatric studies:

The Applicant has submitted sufficient evidence from the published medical literature to address the PREA requirement for this supplemental application. The Applicant has demonstrated that Mifeprex is safe and effective in postmenarchal females, including those under 17 years of age. (b) (6) concurred with granting a partial waiver under PREA in patients ages birth to 12 years of age who are premenarche.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Changes proposed in this efficacy supplement entailed a number of modifications to the current Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex. See Section 9.4 for full details. The (b) (6) (b) (6) concurs with the (b) (6) (b) (6) evaluation of the REMS modifications, which include:

## Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

- Removal of “under Federal law” from the Prescriber Agreement Form is acceptable (see discussion in Additional Submissions / Issues).
- The term “healthcare providers who prescribe” is preferable to the Applicant’s proposed “(b) (4)” (see discussion in Additional Submissions / Issues).
- It is appropriate to modify the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber’s Agreement to include “hospitalization, transfusion or other serious event.” Under these requirements, healthcare providers report certain adverse events to the Applicant, which then is required to report the adverse events to FDA. FDA has received such reports for 15 years, and it has determined that the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely. For this reason, ongoing reporting by certified healthcare providers to the Applicant of all of the specified adverse events is no longer warranted. It should be noted that the Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience reports.

(b) (6) concurs with the following modifications recommended by (b) (6)

- Removal of the Medication Guide (MG) from the REMS. The MG will remain a required part of labeling and will be required to be provided to patients consistent with the requirements in 21 CFR part 208. FDA has been maintaining MGs as labeling but removing them from REMS when, as here, inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks, such as when the MG is redundant and not providing additional use or information to the patient about the risk(s) the REMS is intended to mitigate. This is consistent with ongoing efforts to streamline REMS by allowing for updates to the MG without need for a REMS modification.
- Removal of the Patient Agreement form (ETASU D). This decision was based on the well-established safety profile of Mifeprex, as well as the fact that the small numbers of practitioners who provide abortion care in the US use informed consent practices that are duplicated of the current Patient Agreement and thus the Patient Agreement is no longer necessary to ensure that the benefits of the drug outweigh the risks.
- Revision of the Prescriber Agreement Form to reflect changes to labeling revisions pursuant to the proposed efficacy supplement, and to improve the flow of the document.
- Revision of the REMS goals to reflect the above changes

#### 1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for postmarket requirements or commitments for this efficacy supplement.



Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

## 2 Introduction and Regulatory Background

### 2.1 Product Regulatory Information

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' (7 weeks) pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments." Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets certain qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments that the then-applicant of the Mifeprex NDA (i.e., the Population Council) agreed to meet:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on Day 14 (compliance with return visit) were incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.
2. A surveillance study on outcomes of ongoing pregnancies.

In addition, the 2000 approval letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco).

### 2.2 Tables of Currently Available Treatments for Proposed Indications

In the US there are no other approved products for the medical termination of first trimester pregnancy. Misoprostol alone or in combination with methotrexate has been used for early medical abortion (MAB), with much lower success than Mifeprex.<sup>1</sup>

---

<sup>1</sup> American College of Obstetricians and Gynecologists. Practice bulletin No. 143: medical management of first-trimester abortion. *Obstet Gynecol* 2014;123(3):676-92. doi:10.1097/01.AOG.0000444454.67279.7d.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

### 2.3 Availability of Proposed Active Ingredient in the United States

Mifepristone: The only other FDA approval for mifepristone is the product Korlym, approved under NDA 202107 on February 17, 2012 for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

### 2.4 Important Safety Issues with Consideration to Related Drugs

Korlym (mifepristone) is indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. Korlym is taken in oral doses of 300 mg to 1200 mg daily. It is contraindicated in pregnancy, patients taking simvastatin, lovastatin and CYP3A substrates with narrow therapeutic ranges, patients on corticosteroids for lifesaving purposes, and women with unexplained vaginal bleeding or endometrial hyperplasia with atypia or endometrial carcinoma. The label<sup>2</sup> provides warnings and precautions regarding adrenal insufficiency, hypokalemia, vaginal bleeding and endometrial changes, QT prolongation, exacerbation or deterioration of conditions treated with corticosteroids, use of strong CYP3A inhibitors, and opportunistic infections with *Pneumocystis jiroveci* pneumonia in patients with Cushing's. Adverse reactions noted in  $\geq 20\%$  of patients in clinical trials with Korlym included nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite and endometrial hypertrophy.

#### Reviewer comment:

**Some of the adverse events noted with Korlym are also seen with Mifeprex, such as nausea and vomiting. However, Korlym is taken in higher doses, in a chronic, daily fashion unlike the single 200 mg dose of Mifeprex that is the subject of this supplement; the rate of adverse events with Mifeprex is much lower.**

Ella (ulipristal acetate) is a progesterone agonist/antagonist emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. The **ella** label<sup>3</sup> notes that in clinical trials, the most common adverse reactions ( $\geq 10\%$ ) in women receiving **ella** were headache (18% overall) and nausea (12% overall) and abdominal and upper abdominal pain (12% overall).

Due to **ella's** high affinity binding to the progesterone receptor, use of **ella** may reduce the contraceptive action of regular hormonal contraceptive methods. The label notes that after **ella** intake, menses sometimes occur earlier or later than expected by a few

<sup>2</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/202107s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202107s000lbl.pdf)

<sup>3</sup> [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/022474s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf)

## Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

days. In clinical trials, cycle length was increased by a mean of 2.5 days but returned to normal in the subsequent cycle. Seven percent of subjects reported menses occurring more than 7 days earlier than expected, and 19% reported a delay of more than 7 days. The label recommends that women rule out pregnancy if the expected menses is delayed by more than one week. Nine percent of women studied reported intermenstrual bleeding after use of ella.

**Reviewer comment:**

**Ella is for occasional use and is not to be used as a regular contraceptive method. As such, the drug is not recommended for repeated use in the same menstrual cycle. The safety and efficacy of repeat use within the same cycle has not been evaluated. A single dose of ella does not appear to result in serious adverse events.**

**2.5 Summary of Presubmission Regulatory Activity Related to Submission**

A pre-NDA meeting was held with the Applicant on January 29, 2015. The following items, among others, were discussed:

- New dosing regimen
- Proposal to have (b) (4)
- Use up to (b) (4) days' gestation
- Change in the interval between Mifeprex and misoprostol administration to 24-48 hours
- Revision of the labeled time to expulsion after misoprostol is administered
- Use of the term "(b) (4)" in the approval and label to describe who may obtain and dispense Mifeprex
- Deletion of "under Federal law" in the Prescriber's Agreement
- PREA requirements
- Regulatory pathway for approval

**2.6 Other Relevant Background Information**

Since the approval in France and China in 1988, mifepristone for MAB is currently approved in 62 countries globally<sup>4</sup>; see the list and dates of approval in Appendix 9.7.

Prior to the Mifeprex approval by the FDA, mifepristone had also been approved in the UK in 1991. In the UK, the current therapeutic indications include:

- Medical alternative to surgical termination of intrauterine pregnancy up to 63 days gestation based on the first day of the last menstrual period
- Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination during the first trimester

<sup>4</sup> Gynuity website, [www.gynuity.org](http://www.gynuity.org), Medical Abortion in Developing Countries- List of Mifepristone Approvals.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

- For use with prostaglandin analogues for termination of pregnancy for medical reasons beyond the first trimester
- Labour induction in foetal death in utero<sup>5</sup>

The estimated cumulative use of Mifeprex in the US since the 2000 approval is 2.5 million uses. Estimated global occurrence of MAB and SAB combined was 43.8 million abortions in 2008 (Guttmacher Institute data)<sup>6</sup>. MAB has been increasingly used as its efficacy and safety have become well-established by both research and experience, and serious complications have proven to be extremely rare.<sup>7</sup> Medical abortion comprises 16.5% of all abortions in the US, 25.2% of all abortions at or before 9 weeks of gestation<sup>1</sup>, and based on data from 40 reporting areas sending data to the CDC, 30.8% of all abortions at or before 8 weeks gestation (2012 data).<sup>8</sup> In 2011, approximately 239,400 medical abortions were performed, which was a 20% increase from 2008 data.<sup>9</sup> Data show that in the most recently reported 12 months (September 29, 2014-September 28, 2015), (b) (4) Mifeprex tablets were distributed in the US (NDA 20687 SD # 650, Annual Report-15, submitted October 09, 2015). Further, the vast majority of practitioners in the US who provide medical abortion services use a regimen other than the FDA-approved one. In 2008, Wiegerinck et al published a survey of members of the National Abortion Federation which showed that only 4% of facilities were using the current FDA-approved regimen.<sup>10</sup>

It is noteworthy that ten years ago, the combination of mifepristone and misoprostol for medical abortion was included on the World Health Organization (WHO) Model list of Essential Medicines for termination of pregnancy where legal and acceptable, up to 9 weeks of gestation.<sup>11</sup> Several other national and international organizations have also endorsed the safe use of medical abortion up to 9 and 10 weeks of gestation. This topic will be discussed thoroughly in the Efficacy and Safety Sections.

<sup>5</sup> Mifegyne Summary of Product Characteristics. Exelgyn Laboratories- June 2013.  
<https://www.medicines.org.uk/emc/medicine/617>

<sup>6</sup> Sedgh G et al., Induced abortion: incidence and trends worldwide from 1995 to 2008. *Lancet*, 2012;379:625-32.

<sup>7</sup> Cleland K, Smith N. Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data. *Contraception* 2015;92:179-81.

<sup>8</sup> Pazol K, Creanga AA, Zane SB, Burley KD, Jamieson DJ. Abortion surveillance--United States, Centers for Disease Control and Prevention (CDC). *MMWR Surveill Summ* 2012;61(SS-8):1-44 and *Surveillance Summaries* Nov 27, 2015; 64(SS10):1-40.

<sup>9</sup> Jones RK, Jerman J. Abortion incidence and service availability in the United States, 2011. *Perspectives on Sexual and Reproductive Health* 2014;46(1):3-14. doi10.1363/46e0414.

<sup>10</sup> Wiegerinck MMJ, Jones HE, O'Connell, K, Lichtenberg ES, Paul M, Westhoff CL. Medical abortion practices: a survey of National Abortion Federation members in the United States. *Contraception* 2008;78:486-491.

<sup>11</sup> World Health Organization April 2015 Model Lists of Essential Medicines Available online at <http://www.who.int/medicines/publications/essentialmedicines/en/>.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

MAB is a choice that women have available in many areas, especially urban, in the US, although it should be noted that some geographical areas in the US have very limited availability of both the surgical and medical options or even one option for early pregnancy termination.

The primary advantages of having a MAB compared to a surgical abortion (SAB) are the following:

- Limited or no anesthesia
- Limited likelihood of any surgical intervention

**Reviewer's Comment:**

**A very small number of physicians currently provide early medical terminations. In the most recent REMS update from the Applicant (stamp date June 3, 2015), the cumulative number of certified prescribers since 2000 is only (b) (4). Between May 1, 2012 and April 30, 2015, the number of new prescribers was (b) (4) and the number of prescribers ordering Mifeprax was (b) (4) during this 3-year period. The number of healthcare providers that are performing early SAB is not documented.**

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

Because this submission did not rely on datasets from any of the clinical trials, no FDA inspections were performed at clinical sites. The authors of the numerous articles, however, have published widely in peer-reviewed medical journals.

#### **3.2 Compliance with Good Clinical Practices**

This submission relies on findings from the published medical literature. The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent.

#### **3.3 Financial Disclosures**

None were submitted or required.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls (CMC)

On March 10, 2016, a separate supplement approved the packaging of a single 200 mg tablet of mifepristone compared to the current 3 tablets in a blister pack. Each packet will have an individual barcode.

#### **Reviewer comment:**

**The approval of single tablet packaging should make recording the barcode of the mifepristone tablet in the patient record (as provided in the REMS) easier as the new proposed dosing regimen uses only one 200 mg mifepristone tablet compared to the previously approved regimen of three tablets.**

(b) (6), reviewed the PLR conversion of the label. Her review, dated January 11, 2016 states the following:

“No changes have been made in the approved chemistry, manufacturing and controls. The approved 200 mg tablet will be used. This review evaluates the PLR conversion of the labeling. Sections 3, 11, and 16 of the PLR labeling, and the Highlights of Prescribing Information, have been evaluated from a chemistry perspective.

**Overall Evaluation:** Acceptable. The labeling provided in Section 3, Section 11, and Section 16, and the Highlights of Prescribing Information, is identical in content to the approved information. The PLR conversion labeling, therefore, is acceptable from a chemistry perspective. The PLR label also corresponds to the content and format required in 21 CFR 201.57.

#### **Reviewer comment:**

**We agree with the conclusions in the CMC review of the PLR conversion of the label.**

### 4.2 Clinical Microbiology

The chemistry (CMC) reviewers determined that a microbiology review was not needed for this efficacy supplement.

### 4.3 Preclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology review by (b) (6), dated March 2, 2016. No preclinical data were submitted for this efficacy supplement. The reviewer's only recommendations were labeling changes. His comments were conveyed to the Sponsor.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

Per (b) (6) review, the supplement is approvable from a Pharmacology/Toxicology standpoint.

#### 4.4 Clinical Pharmacology

The Clinical Pharmacology review by (b) (6) concluded with the following recommendation:

“(b) (6), (b) (6) has reviewed the available clinical pharmacology information in relation to the newly proposed regimen for Mifeprex<sup>®</sup>. We find the application to be acceptable from a Clinical Pharmacology perspective, provided that an agreement on the language in the package insert is reached between the Sponsor and the Division.”

No postmarketing commitments or requirement are recommended.

##### 4.4.1 Mechanism of Action

The original approved label states:

“The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

.....During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.”

##### 4.4.2 Pharmacodynamics

No new studies were submitted with this Application. See the original approved label.

##### 4.4.3 Pharmacokinetics

(b) (6) review states the following:

The pharmacokinetics (PK) of 200 mg mifepristone tablet has not been characterized in women. However, the PK data of 200 mg mifepristone tablet in men are available (1996 study): the mean maximum concentration ( $C_{max}$ ) ( $\pm$  standard error) = 1.77 ( $\pm$ 0.23) mg/L, the mean time to reach  $C_{max}$  ( $T_{max}$ ) = 0.81 ( $\pm$ 0.16) hour, and the mean area-under-the curve (AUC) = 25.8 ( $\pm$ 2.2) mg·h/L. While the effects of sex on the disposition of mifepristone have not been evaluated using Mifeprex<sup>®</sup>, no sex differences in PK of mifepristone were seen with 300 mg mifepristone in a different NDA review (Korlym<sup>™</sup>, NDA 202107, Clinical Pharmacology review). Therefore, Section 12.3 of the proposed label in a PLR format should include the available PK data of mifepristone 200 mg tablet.

Cytochrome P450 3A4 (CYP3A4) plays an important role in the metabolism of mifepristone. Therefore, concomitant intake of CYP3A4 inducers with mifepristone

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

is anticipated to have a significant effect on the disposition of mifepristone. However, the Sponsor did not conduct any *in vivo* studies to evaluate the effect of CYP3A4 inducers on the PK of Mifeprex<sup>®</sup>. Although the lowest effective therapeutic margin of mifepristone for termination of pregnancy has been not characterized clearly, the use of misoprostol in the regimen for Mifeprex<sup>®</sup> contributes to efficacy for inducing termination of pregnancy. In addition, concomitant intake of CYP3A4 inducers does not appear to affect the systemic exposure of misoprostol. In the proposed new regimen, another dose of misoprostol can be administered following day 7 to 14 of post-treatment of mifepristone if termination of pregnancy does not occur.

In summary, the contribution of misoprostol in termination of pregnancy and additional dosing option of misoprostol may compensate the possibly diminished efficacy of Mifeprex<sup>®</sup> in the users of CYP3A4 inducers. However, the labeling information should include the practical clinical guidance for the subject who has been exposed to CYP3A4 inducers.

**Reviewers comments:**

- **We agree with the Clinical Pharmacology conclusions and recommendations made by (b) (6).**
- **Within the last 10 years, administration of oral mifepristone followed by buccal misoprostol for early medical abortion has become the standard of care for MAB in many countries, including the US. This is based on 1) the PK profile of different doses and routes of administration for misoprostol, and 2) many clinical trials comparing the efficacy and safety of different dosing regimens.**

**From Chen and Creinin (2015)<sup>12</sup>:**

**“With buccal administration, misoprostol is held in the buccal pouch between the teeth and gums for 30 minutes before swallowing any remaining tablets. Buccal misoprostol is slowly absorbed, unlike oral misoprostol, which is rapidly absorbed and undergoes extensive first-pass metabolism. After a dose of oral misoprostol, plasma misoprostol acid levels peak quickly at 30 minutes and decrease rapidly by 120 minutes. In contrast, after buccal administration, plasma misoprostol acid levels rise gradually to peak concentration after a median time of 75 minutes and fall slowly over several hours.”**

---

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

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

**The PK profile of vaginal misoprostol is very similar to that of buccal misoprostol. These pharmacological differences between vaginal and buccal misoprostol do not have a clinically meaningful effect on the efficacy at different gestational weeks and the adverse event profile for the combination of mifepristone and misoprostol for early medical abortion. Those routes with rapid and significant absorption (e.g., sublingual) also have high efficacy (ACOG Bulletin<sup>1</sup>). This review, however, focuses primarily on the new dosing regimen proposed by the Applicant with some supportive data from studies that used vaginal and sublingual misoprostol.**

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

There were many studies that provided data for this NDA review. The original US trial that was reviewed for the Mifeprex approval in 2000 was performed over 20 years ago in 1994-95. Subsequently, there has been 20 years of experience with MAB, guidelines from professional organizations here and abroad, and clinical trials that have been published in the peer-reviewed medical literature. This review focuses on the information submitted by the Applicant for the change in the dosing regimen and follow-up.

For a complete list of all sources of information, see the extensive list of references in Appendix 9.6 at the end of this review.



(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

**Table 1: List of Major Studies Reviewed**

USA	International
Gatter 2015 <sup>13</sup> , retrospective	Louie 2014 <sup>14</sup> , Azerbaijan, prospective
Ireland 2015 <sup>15</sup> , retrospective	Ngoc 2014 <sup>16</sup> , Vietnam, prospective
Chong, 2015 <sup>17</sup> , prospective single-arm	Raymond 2013 <sup>18</sup> , International, including US, retrospective
Winikoff 2012 <sup>19</sup> , prospective	Goldstone 2012 <sup>20</sup> , Australia, retrospective
Perriera 2010 <sup>21</sup> , prospective	Boersma 2011 <sup>22</sup> , Curacao, prospective
Winikoff 2008 <sup>23</sup> , RCT*	Middleton 2005 <sup>24</sup> , prospective
Creinin 2007 <sup>25</sup> , prospective	Spitz 1998 <sup>26</sup> , single arm trial

<sup>13</sup> 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.

<sup>14</sup> 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.

<sup>15</sup> 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.

<sup>16</sup> 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.

<sup>17</sup> Chong E, Frye LJ, Castle J, Dean G, Kuehl L, Winikoff B. A prospective, non-randomized study of home use of mifepristone for medical abortion in the US. *Contraception* 2015;92:215-291.

<sup>18</sup> Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87(1):26-37.

<sup>19</sup> 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.

<sup>20</sup> 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.

<sup>21</sup> Perriera LK, Reeves MF, Chen BA, Hohmann HL, Hayes J, Creinin MD. Feasibility of telephone follow-up after medical abortion. *Contraception* 2010;81:143-149.

<sup>22</sup> 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.

<sup>23</sup> 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.

<sup>24</sup> 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.

<sup>25</sup> Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Medical Abortion at the Same

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

Source: compiled by clinical reviewers. \*Randomized controlled trial.

**Reviewer's comment:**

Table 1 above lists the major studies and review articles covering over 45,000 women who had an early MAB through 70 days gestation. Both retrospective and prospective studies were found to be valuable for this review. There are additional studies submitted by the Applicant that are not quoted or reviewed primarily because they did not use a dosing regimen relevant to that proposed by the Applicant or did not contain information pertinent to the other requested changes (e.g., less restrictive follow-up requirements or gestations through 70 days) in the NDA supplement. In some cases, studies that used variants of the proposed regimen were considered because PK, PD and clinical data indicate the relevance of data on vaginally-administered misoprostol, and because lower doses and certain other routes of administration of misoprostol are expected to have lower or similar levels of effectiveness.

**5.1.1 Submissions during the Review Process**

During the course of the review, the Applicant submitted additional supportive articles from the peer-reviewed medical literature, and provided more detailed data from previously submitted articles based on direct communication with the authors. Further, the Applicant submitted changes to some of the original proposals. Below in Table 2 is a list of the clinical submissions to the NDA after the initial submission dated May 18, 2015.

---

Time (MAST Study Trial Group). Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion a randomized controlled trial. *Obstet Gynecol* 2007;109:885-894.

<sup>26</sup> Spitz IM, et al. Early Pregnancy Termination with Mifepristone and Misoprostol in the United States. *NEJM* 1998;338(18):1241-47.

Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

**Table 2 Clinical Submissions during the Course of the Review**

Item	Submission Type, Date
Additional supportive articles More detailed data from previously submitted articles	Amendment # 3, dated 9/23/2015 Amendment # 4, dated 10/13/2015 Amendment # 5, dated 11/16/2015 Amendment # 6, dated 12/8/2015
Additional supportive documents on patient counseling	Follow-up to 1/27/2016 teleconference, dated 2/2/2016
Additional supportive articles	Amendment # 8, dated 2/25/2016
<b>Proposed Additional Changes</b>	
REMS amendment, Revised REMS Supporting Document Additional supportive articles	Amendment # 2, dated 7/16/2015
REMS modification	Dated 11/4/2015
Labeling: (b) (4) Indication Statement	Amendment # 4, dated 10/13/2015
Labeling changes: (b) (4) the proposed new dosage regimen (b) (4)	Follow-up to 1/27/2016 teleconference, dated 2/15/2016, Also in Amendment # 9, dated 2/25/2016
Labeling: changes to Sections 2.4, 5.2, 6.1, 7, 8.1, 8.2, 8.6, 12.3, 14	Amendment # 7, dated 2/23/2016
Labeling changes: revise indication statement to state "through 70 days gestation"	Amendment # 9, dated 2/25/2016
Labeling: changes to Sections 2.3, 6.1 and 14	Amendment # 10, dated 3/17/2016
REMS documents	Amendment #11, dated 3/21/2016

Source: Reviewer table.

## 5.2 Review Strategy

This is a joint review by two medical officers: (b) (6) reviewed the efficacy data and (b) (6) reviewed safety data and related issues. Other sections are jointly completed.

Within the last 10 years, use of buccal misoprostol with mifepristone for MAB has become commonplace. However, the published literature did not contain abundant information about medical abortion outcomes with buccal misoprostol at the time of the



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

original NDA review. In this review, we summarize clinical outcomes and adverse effects of medical abortion regimens consisting of oral mifepristone 200 mg followed in 24-48 hours by buccal misoprostol 800 mcg in pregnancies through 70 days of gestation.

### 5.2.1 Discussion of Individual Studies/Clinical Trials

Information and findings from individual clinical trials and reviews in the published medical literature, websites, the Applicant and other sources are discussed in different sections throughout this review. As acknowledged during pre-submission discussions between the Applicant and (b) (6) and as is typical for literature-based submissions, original datasets from the trials that are cited were not available for submission in this supplement.

## 6 Review of Efficacy

### Efficacy Summary

**This summary lists the final conclusions based on review of the data. Not all of the conclusions, regarding covariates such as ethnicity, parity, previous abortion, are specifically addressed in labeling, but the reviewers believe that it is important to show that we evaluated many different aspects and potential risk factors for safe and effective MAB:**

- Medical termination of pregnancies through 70 days gestation is safe and effective and should be approved using the new proposed regimen.
- The original approved dosing regimen remains safe and effective but the new proposed dosing regimen is effective and should be approved for use in gestations through 70 days (10 weeks) gestation.
- 2015 Chen-Creinin review<sup>12</sup> of over 33,800 MABs concluded that regimens with a 24-hour time interval between mifepristone and buccal misoprostol administration are slightly less effective (94.2% success) compared to those with a 24-48-hour interval (96.8% success).
- 2013 Raymond review<sup>18</sup> of over 45,500 MABs using oral mifepristone 200 mg and various misoprostol doses concluded that the effectiveness decreases when:
  - misoprostol is taken orally compared to the three other routes of administration (buccal, sublingual, or vaginal)
  - the gestational age increases
  - the mifepristone-misoprostol interval is less than 24 hours
  - the total misoprostol dose is 400 mcg or less
- Efficacy in the adolescent population is the same or slightly better compared to non-adolescent women.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

- Efficacy outcomes do not appear to be related to other baseline characteristics including age, race, body weight, gravidity and previous spontaneous abortions. (Spitz data<sup>26</sup> and many subsequent studies)
- Data from the original US trial (1994-95; Spitz 1998<sup>26</sup>) showed lower efficacy rates with the originally approved Mifeprex dosing than is reported in a large number of subsequent trials using different mifepristone-misoprostol dosing regimens for early MAB. There does not appear to be any change in the safety profile.
- Raymond (2013 systematic review<sup>18</sup>) found no significant association between abortion failure rates and the timing of the follow-up evaluation.
- Over 30% of women will completely expel the products of conception within 4-5 hours of taking the misoprostol for MAB with gestations of 57-70 days (Winikoff 2012<sup>19</sup>); this finding supports the proposal to allow women to choose the timing of (within the labeled range) and where to take the misoprostol.
  - Data from the original NDA review showed occurrence of a successful (complete) MAB occurred in  $\leq 4$  hours after misoprostol administration in 45-46% of women up to 56 days gestation and 34.9% of women at 57-63 days gestation.
- Home administration of misoprostol is efficacious, practical, and safe (see Safety Section)

**Reviewer’s overall comment:**

**Compared to the current Mifeprex approved label and regimen, the Applicant has requested less restrictive measures for location and timing of misoprostol administration and follow-up measures for early MAB. We believe that a regimen that includes these less restrictive measures is equally safe and effective, while offering women greater convenience and providing a less burdensome procedure for patients and providers.**

**6.1 Indication**

In the initial submission of this efficacy supplement, the proposed new indication was the following: “Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (b) (4)” In Amendment # 9, submitted on February 25, 2016, the Applicant proposed (b) (4) the gestational age through 70 days.

The proposed new modified regimen uses buccal (not oral) misoprostol administered 24-48 hours after taking a lower dose, 200 mg instead of 600mg, of oral mifepristone. The labeled dose of misoprostol is increased compared to the current approved regimen, from 400 mcg to 800 mcg. (b) (4)

(b) (4)  
(b) (4)  
(b) (4), the

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

(b) (4)

These requests were thoroughly reviewed by the Agency and we believe the product is safe and effective for the indication, which reads:

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

### **6.1.1 Methods**

There were numerous articles from the peer-reviewed medical literature that were submitted by the Applicant. Articles were also cited in three letters sent to CDER Center Director Janet Woodcock, MD from 1) ACOG, 2) a group of academic professionals and women's health non-profit organizations, and 3) thirty professional and academic organizations, all of which requested changes to the Mifeprex labeling and REMS. All relevant publications cited in those three letters were also submitted by the Applicant for our review. The articles and sources of data used for this review are listed in the Reference List in Appendix 9.6 at the end of this review.

The various studies noted in the articles had slightly different designs, inclusion criteria, dosing regimens and endpoints for safety and efficacy. The review focus is on clinical trials and follow-up methods for early medical abortion, including gestations through 70 days (10 weeks).

### **6.1.2 Demographics**

Many of the trials were randomized and some were blinded to the actual dose of the two drugs that were administered. The route of misoprostol administration could not be easily blinded. Although there may have been some small differences in the demographic data for the different arms, it is doubtful that demographic differences such as race or ethnicity are clinically meaningful in relation to the safety and efficacy of medical abortion.

### **6.1.3 Subject Disposition**

Most of the studies noted the number of women who were lost to follow-up and did not count them in the efficacy analysis. All women with any available safety data were included in the safety analyses. See Safety Section for further discussion.

### **6.1.4 Analysis of Primary Endpoint(s)**

The studies analyzed for data used in this NDA review almost universally defined their primary efficacy endpoint as expulsion of the pregnancy from the uterus without need for any surgical evacuation or procedure for any reason (including patient request).



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

### 6.1.5 Analysis of Secondary Endpoints(s)

In addition to the final outcome of MAB success or lack of success (i.e., surgical or medical intervention needed), there are intermediate outcomes:

- Incomplete abortion: pregnancy no longer ongoing, but only partial or non-expulsion of the products of conception has occurred
- Ongoing pregnancy based on fetal heartbeat and/or growth

In the case of incomplete expulsion but where the pregnancy is no longer ongoing, there are in the US several safe options available to the healthcare provider and the patient:

- Expectant management (in many cases, complete expulsion will occur spontaneously given additional time)
- Additional dose of misoprostol
- Minor surgical procedure such as a vacuum aspiration in the clinic/office
- Surgical procedure under anesthesia such as a dilation and curettage (D&C)

For ongoing pregnancies following the initial MAB procedure, typically one of the surgical procedures is performed.

In addition to these two intermediate outcomes, there are other cases in which a surgical intervention might be performed:

- Intervention because of bleeding or other aspect of the patient's condition: the healthcare provider judges that surgical intervention is indicated
- Patient request: the patient requests surgical intervention for any reason

### 6.1.6 Proposal for a New Dosing Regimen

There are five major changes proposed by the Applicant in this supplement for which efficacy data will be discussed. The changes are interrelated and, in general, the same studies usually provide evidence to support multiple changes, although data from a given study may be more or less pertinent to a specific change (e.g., extending the approved gestational age, home administration of buccal misoprostol, etc.).

#### **Summary of changes to dosing regimen, indication, and follow-up initially requested by the Applicant in the NDA Supplement:**

1. **Addition of a new dosing regimen of Mifeprax 200 mg orally followed by the buccal administration of 800 mcg misoprostol at 24-48 hours instead of 48 hours**
2. **Increase in gestational age from (b) (4)**
3. **Option to administer misoprostol outside of the clinic**

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

4. **Option that a repeat dose of misoprostol may be used if needed for women using the new proposed dosing regimen**
5. **Follow-up timing and methods: follow-up is needed at 7-14 days after Mifeprex administration; the specific nature and timing of the follow-up to be agreed upon by the (b) (4) and patient. The current approved label states: “Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex.”**

Discussion and analysis of the data supporting the five changes follows in five individual sections.

**1. Proposal of a new dosing regimen that:**

- 1) **decreases the oral dose of Mifeprex from 600 mg to 200 mg orally,**
- 2) **increases the misoprostol dose from 400 mcg orally to 800 mcg misoprostol administered buccally, and**
- 3) **revises the interval between Mifeprex and misoprostol dosing from 48 hours to “24-48 hours.”**

(b) (4)

Background on some dosing data and US practices:

There is ample medical evidence that the currently approved dose regimen (oral mifepristone 600 mg followed 2 days later with oral misoprostol 400 mcg) is safe and efficacious up to 49 days gestation. It was approved in September 2000 based on the US clinical trial of 1994-95 and two French trials. After 1995, however, more studies gradually became available using lower doses of mifepristone and different doses and routes of administration for misoprostol. These newer data were not submitted to or considered in the original NDA review. Studies also showed that with lower doses (< 600 mg) of oral mifepristone followed by oral misoprostol 400 mcg, the treatment success rate is greater than 95% up to 49 days gestation.

It is difficult to tell how many MABs in the US actually used the FDA-approved dosing regimen following the 2000 approval. It is clear that many clinics and individual practitioners did not. For example, from 2001 to March 2006, Planned Parenthood Federation of America (PPFA) health centers throughout the United States provided medical abortions principally using a regimen of oral mifepristone 200 mg, followed 24–48 hours later by 800 mcg misoprostol administered vaginally at home.<sup>27</sup> Of note, PPFA has been and continues to be the largest provider of MAB services in the US.

<sup>27</sup> Fjerstad M, Sivin I, Lichtenberg ES, Trussell J, Cleland K, Cullins V. Effectiveness of medical abortion

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

**Reviewer's comment:**

**The 2009 Fjerstad article<sup>28</sup> states that PPFA was a federation of 97 independent local affiliates operating 880 health centers throughout the US; roughly 300 of those centers provided medical abortion. So, within one year of the FDA Mifeprax approval, PPFA was using a dosing regimen (actual doses and routes of administration) very similar to that proposed in this efficacy supplement.**

Meanwhile, from September 2003 to June 2005, there were four fatalities in the US and one in August 2001 in a Canadian clinical trial, all due to a sudden and rapid sepsis secondary to the bacteria *Clostridium sordellii*. The five cases were with early MAB (all around 7 weeks gestation) in women who had used 800 mcg vaginal misoprostol. By late March 2006, consideration of these fatal uterine infections led PPFA to 1) change the route of administration of the 800 mcg misoprostol from vaginal to buccal (or, much less commonly, oral) and 2) employ additional measures (sexually transmitted infection [STI] testing and treatment if positive, or use of prophylactic antibiotics) to minimize the risk of subsequent serious uterine infections. In July 2007, PPFA began requiring routine treatment with antibiotics for all medical abortions at their health centers.<sup>28</sup>

**Reviewer's comment:**

**As stated in currently approved labeling “No causal relationship between the use of Mifeprax and misoprostol and these events [serious and sometimes fatal infections and bleeding] has been established.” There is no clear evidence that the vaginal use of misoprostol causes infection, and no causal association has been identified between the cases of sepsis and vaginal administration of misoprostol. While labeling was revised in November 2004 and July 2005 to recommend that providers have a high index of suspicion in order to rule out serious infection and sepsis, the Agency did not consider there was sufficient evidence to justify recommending prophylactic antibiotics.**

A 2006 article showed that in pregnancies greater than 49 days gestation, compared to oral administration of misoprostol, the bioavailability and efficacy with use of misoprostol is increased by vaginal, sublingual and buccal administration, avoiding first-pass metabolism by the liver.<sup>29</sup> Furthermore, a 2009 review of MAB<sup>30</sup> noted that:

“Consistent with other kinetic studies, clinical trials have demonstrated no change in efficacy when mifepristone doses are reduced from 600 to 200 mg. Multiple

---

with mifepristone and buccal misoprostol through 59 gestational days. Contraception 2009;80:282-6.

<sup>28</sup> Fjerstad M, Trussell J, et al. Rates of serious infection after changes in regimens for medical abortion. NEJM 2009;361:145-51.

<sup>29</sup> Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with prostaglandin analogue. Contraception 2006;74:66-86.

<sup>30</sup> Bartz B, Goldberg A. Medical Abortion. Clin Obstet and Gyn 2009; 52:140-50.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

clinical studies, including a 2004 Cochrane meta-analysis, reported that a regimen of 200 mg of oral mifepristone followed 24 to 48 hours later by 800 mcg of vaginal misoprostol results in complete abortion in 96% of cases at gestations of up to 63 days and that increasing the mifepristone dose to 600 mg does not improve efficacy.”

In a 2010 review article covering 25 years of the clinical development of mifepristone followed by a prostaglandin for MAB, Spitz<sup>31</sup> noted similar conclusions:

“In the US, most investigators administer 200 mg rather than 600 mg mifepristone as many trials have shown equivalent results with these two dose schedules. A recent meta-analysis of four randomized controlled trials compared the two dose regimens. Endpoints were complete abortion, continuing pregnancy and side effects. The two doses [600 v. 200 mg mifepristone] result in similar rates of complete abortion with no difference in adverse events.”

Another change in clinical practice was related to the labeling stipulation that women return to the clinic/office two days after Mifeprex was administered to take the misoprostol dose. Many experts involved with termination of early pregnancies also advocated misoprostol self-administration at home to mitigate the time, travel and inconvenience of this additional visit.

In the US, the American College of Obstetricians and Gynecologists (ACOG), National Abortion Federation<sup>32</sup>, and PPFA currently all endorse the lower oral dose of mifepristone followed in 24-48 hours with misoprostol. According to the 2014 ACOG Practice Bulletin, the misoprostol route of administration may be oral, buccal, sublingual or vaginal; sublingual administration, however, has a more rapid absorption resulting in a higher incidence of adverse side effects.<sup>1</sup>

#### European practice:

In December 2011, the International Federation of Obstetrics and Gynaecology (FIGO) published revised guidelines for the use of mifepristone and misoprostol for MAB up to 63 days, 64-84 days, and after 84 days (12 weeks) gestation.<sup>33</sup> The FIGO recommended regimens using 200 mg of oral mifepristone followed by 800 mcg of misoprostol administered vaginally, buccally, or sublingually. Up to 57-63 days gestational age, misoprostol is taken 24-48 hours after mifepristone. Per the review of data available to them, FIGO decided additional doses of 400 mcg misoprostol may be

---

<sup>31</sup> Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. *Contraception* 2010;82:442–52.

<sup>32</sup> National Abortion Federation Guidelines 2015.

<sup>33</sup> Faundes A. The combination of mifepristone and misoprostol for the termination of pregnancy. *Int J Gynecol Obstet* 2011;115:1-4.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

safely used depending on gestational age, and these combinations result in a complete termination in more than 95% of cases.

Similar guidelines using either vaginal, buccal, or sublingual misoprostol are endorsed by the World Health Organization (WHO), the United Kingdom Royal College of Obstetricians and Gynecologists<sup>34</sup>, and a recent Cochrane Review (2011, Issue11).<sup>35</sup>

**Reviewer's Comment:**

**From the above discussion, it is clear that the standard of care in the US for early MAB has deviated from the FDA-approved dosing regimen. PPFA provides the largest number of medical abortions each year in the US and as early as 2001, was already using the regimen of 200 mg oral mifepristone followed 24-48 hours later by 800 mcg vaginal misoprostol.**

There are a large number of studies and reviews that support the efficacy of the proposed new dose regimen through 63-70 days gestation. Efficacy was defined in these studies as a complete expulsion of the pregnancy without need for surgical intervention for any reason during the follow up period. The 2015 review by Chen and Creinin summarized clinical outcomes and adverse effects from 20 MAB studies including a total of 33,846 women using regimens consisting of 200 mg oral mifepristone followed by buccal misoprostol through 70 days gestation. All studies except two used 800 mcg misoprostol. Two studies (827 women) used 400 mcg buccal misoprostol. Six studies used a 24-hour time interval between mifepristone and buccal misoprostol administration and 14 used a 24-48 hour window for the dosing interval. The table below lists the 15 studies using the proposed doses (200 mg plus 800 mcg) with a 24-48 hour dosing interval.

---

<sup>34</sup> Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline Number 7. 3rd ed. London (UK):RCOG Press 2011.

<sup>35</sup> Kulier R, Kapp N, et al. Medical methods for first trimester abortion (Review). The Cochrane Library 2011, Issue 11:1-126.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex**Table 3: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later - US Studies**

Study & Year	Design, Location	Gestation (maximum days)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Middleton 2005 <sup>24</sup> US	Prospective	56	24-48	216	94.9
Winikoff 2008 <sup>23</sup> US	Prospective	63	24-36	421	96.2
Fjerstad 2009 <sup>27</sup> US	Retrospective	59	24-48	1,349	98.3
Grossman 2011 <sup>36</sup> US - Clinic Mife v. Tele-med	Prospective	63	24-48	449	Clinic: 96.9% Telemed: 98.7%
Winikoff 2012 <sup>19</sup> US	Prospective	57-70	24-48	629	93.2
Gatter 2015 <sup>13</sup> US	Retrospective	63	24-48	13,373	97.7
Chong 2015 <sup>17</sup> US	Prospective	63	24-48	357	96.7
<b>TOTALS</b>	<b>7 Studies</b>	<b>56-70 days</b>	<b>24-48 hr</b>	<b>16,794</b>	<b>97.4</b>

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

<sup>36</sup> Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

**Table 4: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later- Non- US Studies**

Study &Year/Country	Design, Location	Gestation (maximum)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Alam 2013 <sup>37</sup> Bangladesh	Prospective	63	24	629	92.7
Blum 2012 <sup>70</sup>	Prospective	63	24	210	92.9
Boersma 2011 <sup>22</sup> Curacao	Prospective	70	24-48	307	97.7
Chai 2013 <sup>38</sup> Hong Kong	Prospective	63	48	45	95.6
Dahiya 2012 <sup>39</sup> India	Prospective	50	24	50	92
Chong 2012 <sup>40</sup> Georgia, Vietnam	Prospective	63	36-48	560	96.4
Giri 2011 <sup>41</sup> Nepal	Prospective	63	24	95	93.6
Goldstone 2012 <sup>20</sup> Australia	Retrospective	63	24-48	11,155	96.5
Louie 2014 <sup>14</sup> Azerbaijan	Prospective	63	24-48	863	97.3
Ngo 2012 <sup>42</sup> China	Retrospective	63	36-48	167	91.0
Ngoc 2011 <sup>43</sup> Vietnam	Prospective	63	24	201	96.5
Ngoc 2014 <sup>16</sup> Vietnam	Prospective	63	24-48	1,371	94.7
Olavarietta 2015 <sup>85</sup> Mexico	Prospective	70	24	884	98.2
Pena 2014 <sup>44</sup> Mexico	Prospective	70	24-48	971	97.3

<sup>37</sup> Alam A, Bracken H et al. Acceptability and Feasibility of Mifepristone-Misoprostol for Menstrual Regulation in Bangladesh. *Intrnational Persp on Sexual and Reprod Health* 2013;39(2):79-87.

<sup>38</sup> Chai J, Wong CY, Ho PC. A randomized clinical trial comparing the short-term side effects of sublingual and buccal routes of misoprostol administration for medical abortions up to 63 days' gestation. *Contraception* 2013;87:480-5.

<sup>39</sup> Dahiya K, Ahuja K, Dhingra A et al. Efficacy and safety of mifepristone and buccal misoprostol versus buccal misoprostol alone for medical abortion. *Arch Gynecol Obstet* 2012; 285: 1055-8

<sup>40</sup> Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. *Contraception* 2012;86:251-6.

<sup>41</sup> Giri A, Tuladhar H et al. Prospective study of medical abortion in Nepal Medical College- a one year experience. *Nepal Medical Coll J* 2011;13(3):213-15.

<sup>42</sup> Ngo TD, Park MH, Xiao Y. Comparing the WHO versus China recommended protocol for first trimester medical abortion: a retrospective analysis. *Int J Womens Health* 2012;4:123-7.

<sup>43</sup> Ngoc NTN, et al. Comparing two early medical abortion regimens: mifepristone+misoprostol vs. misoprostol alone. *Contraception* 2011;83:410-17.

<sup>44</sup> Pena M, Dzuba IG, Smith PS, et al. Efficacy and acceptability of a mifepristone-misoprostol combined

## Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

Sanhueza 2015 <sup>48</sup> Mexico	Prospective	70	24-48	896	93.3
<b>TOTALS</b>	<b>15 Studies</b>	<b>56-70 days</b>	<b>24-48 hrs</b>	<b>18,425</b>	<b>96.1%</b>

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

**Reviewer's comments:**

The data above in Table 3 and Table 4 from ~16,800 US women and ~18,400 non-US women in clinical studies of MAB through 70 days gestation with success rates of 97.4% (US) and 96.1% (non-US) strongly support the proposed new dosing regimen and the extension of the acceptable gestational age. The number of US and non-US studies, the number of evaluable women, and the overall complete abortion rates (termination with no surgical intervention) will be described in the efficacy table in Section 14 CLINICAL STUDIES in the new approved label. Additional discussion on increasing the gestational age through 70 days follows in the next major section.

Precise timing of the administration of misoprostol has not been shown to result in a higher success rate which is why the majority of the above studies allowed a range of hours between the mifepristone dose and misoprostol dose rather than one set time between the two drugs. The 2013 Raymond systematic review<sup>18</sup> of 87 studies that exclusively used a mifepristone 200 mg oral dose in over 45,000 women, followed by varying doses and routes of administration of misoprostol, concluded that if the mifepristone-misoprostol interval is < 24 hours, the procedure is less effective compared to an interval of 24-48 hours.

Another study<sup>45</sup> also looked at the question of the mifepristone-misoprostol interval. The authors conducted a systematic review of randomized controlled trials published from 1999 to 2008 to assess the evidence for a shorter mifepristone and misoprostol administration interval for first trimester medical termination. Searching strategy included MEDLINE, EMBASE, CLINAHL and Cochrane Library. The primary outcome measure was complete abortion without the need for a surgical procedure. "Five randomized controlled trials (RCTs) compared the efficacy of mifepristone-misoprostol administration intervals between 0 and 72 hours in 5,139 participants. The complete abortion rates varied between 90% and 98%. Although the meta-analysis of pooled data of all five RCTs showed no statistically significant difference in efficacy between

---

regimen for early induced abortion among women in Mexico City. *Int J Gynaecol Obstet* 2014;127:82-5.

<sup>45</sup> 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.

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

the shorter and longer dosing intervals, there was a trend toward slightly lower success rates with administration intervals < 8 hours.” This study supports the finding that the proposed regimen is effective with the 24-48 hour flexible interval. Labeling will indicate that the regimen may not work as well if the misoprostol is taken earlier than 24 hours after Mifeprex.

**Reviewer’s Final Recommendation:**

**The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol should be approved; there are sufficient data from the medical literature with over 35,000 women supporting the regimen’s efficacy (termination without any additional surgical intervention) as being in the 91-98% range.**

**6.1.7 Increase in gestational age from 49 days to 70 days**

**Original NDA review:**

The US clinical trial<sup>31</sup> was conducted from September 1994 to September 1995 and treated 2,121 women. A total of 2,015 women (95%) returned at the 14-day follow-up visit. The trial categorized women into three groups based on gestational age at the time of procedure, and evaluated the rates of “Success” (a complete pregnancy termination without use of any additional doses of misoprostol or surgical intervention), and the rates of “Failure” (with four sub-categories of incomplete abortion, ongoing pregnancy, intervention for medical reason, and intervention solely because of patient request). The success and failure data are shown in Table 5.

**Table 5: Original NDA Efficacy Results**

OUTCOME	≤ 49 Days N= 827 (%)	50-56 Days N= 678 (%)	57-63 Days N= 510 (%)
Success (mifepristone + misoprostol)	762 (92)	563 (83)	395 (77)*†
<b>Failure (any surgical intervention for any reason) N (%)</b>			
<b>Total failures</b>	<b>8%</b>	<b>17%</b>	<b>23%*†</b>
Incomplete abortion	39 (5)	51 (8)‡	36 (7)
Ongoing pregnancy	8 (1)	25 (4)*	46 (9)* §
Medical indication for intervention	13 (2)	26 (4)‡	21 (4)‡
Patient’s request for intervention	5 (0.6)	13 (2)	12 (2)‡

\*P<0.001 for the comparison with the ≤ 49-days group.

†P= 0.02 for the comparison with the 50 to 56-days group.

‡ 0.001 ≤ P<0.03 for the comparison with the ≤ 49-days group.

§ P<0.001 for the comparison with the 50 to 56-days group.

Source: Modified from Table 1, pg 1243 in the Spitz NEJM article (1998).



Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

**Reviewer's comments:**

Looking at the results in the table above, it is reasonable that the approved use was only for women in the first 49 days' gestation, given the 8% "failure rate" in this subgroup, compared to 17% and 23% failure rates for the longer gestations. It is important to note that failure was defined as any case requiring surgical intervention for any of the following reasons:

- incomplete abortion (incomplete expulsion)
- documented ongoing pregnancy
- medical reasons (usually heavy vaginal bleeding with or without retained products of conception)
- patient request (usually for bleeding)

As has been pointed out, since the US trial data used for the FDA approval of Mifeprex, given the experience and data gained in the last 20 years from millions of women in the US and abroad, the success rates and overall outcomes are very different. Currently, when a "failure" occurs, using the original definition, options that are now commonly available include the following:

- expectant management (wait and see) in the case of an incomplete abortion (i.e., pregnancy terminated but not fully expelled)\*
- medical treatment for bleeding, pain and other common symptoms
- clinical evaluation with the use of 1) office ultrasound and/or 2) hCG data determined by rapid, sensitive urine and/or serum testing\*
- additional doses of misoprostol for an incomplete abortion\*
- less invasive surgical intervention (vacuum aspiration) in the clinic/office instead of a D&C under anesthesia in an operating room
- continuing the pregnancy (although the medical recommendation is to proceed to a surgical abortion in such a case, we acknowledge that a woman could potentially decide to continue the pregnancy)

\* per protocol, these options were NOT available in the original US trial

It is also evident that the proposed new dosing regimen is considerably more effective for all gestations through 70 days [see data and discussion that follows for 57-63 and 64-70 days gestation], especially when compared to the original data using the FDA-approved regimen which had "success" rates of only 83% and 77% at 50-56 and 57-63 days gestation, respectively.

**Current evidence for increasing the gestational age to 70 days**

Current evidence demonstrates that the new proposed medical abortion regimen is effective for women in the range of 57-63 days and 64-70 days of gestation. A 2015

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

systematic review identified six published studies that recorded data on outcomes of medical abortions performed during gestational Days 64-70.<sup>46</sup>

The published studies were conducted in the United States, UK, Mexico, Curaçao, Vietnam, and the Republic of Georgia. All subjects were treated as outpatients between 2007 and 2015. The older UK study evaluated 127 women who were at 64-70 days gestation and treated with 200 mg oral mifepristone followed by 800 mcg vaginal misoprostol.<sup>47</sup>

**Reviewer comment:**

**We evaluated the data separately for 57-63 and 64-70 days of gestation. The following two tables show the efficacy data for 57-63 and 64-70 days gestation (also known as Week 9 and Week 10).**

---

<sup>46</sup> Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70days gestation. *Contraception* 2015;92:197-9.

<sup>47</sup> Gouk EV, et al. Medical termination of pregnancy at 63-83 days gestation. *British J Obstet Gyn* 1999;106:535-539.

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprax

**Table 6: MAB Efficacy Outcome 57-63 Days Gestation**

Study	Enrolled N	Followed N	Success N (%)	Ongoing Pregnancy N (%)	Lost to Follow up %	Comment
Winikoff <sup>23</sup> 2008 US-	132	115	109 (94.8)	2 (1.7)	13.0%	* Proposed Dosing
Winikoff <sup>19</sup> 2012 US	379	325	304 (93.5)	10 (3.1)	14.2%	* Proposed Dosing
Gatter <sup>13</sup> 2015 US	1527	1286	1228 (95.5)	21 (1.6)	15.8%	* Proposed Dosing
Sanhueza <sup>48</sup> 2015 Mexico City	196	190	171 (90.0)	6 (3.2)	3.1%	* Proposed dosing
Boersma <sup>22</sup> 2011** Curacao	105	95	91 (95.8)	2 (2.1)	9.5%	*Proposed dosing @ 24- 36 hr @ home
Pena <sup>44</sup> 2014 Mexico City	177	171	164 (95.9)	2 (1.2)	3.4%	* Proposed dosing
Chong <sup>40</sup> 2012 Viet Nam, Georgia	86	85	79 (92.9)	2 (2.4)	1.2%	*Proposed dosing 36-48 hr
	81	81	77 (95.1)	2 (2.5)	0%	400 mcg buccal @ 36- 48 hr
Bracken <sup>49</sup> 2014 4 countries-	389	382	362 (94.8)	7 (1.8)	1.3% (2 women withdrew)	400 mcg sublingual @ 24-48 hr
<b>TOTAL</b>	<b>3,072</b>	<b>2,730</b>	<b>2,585 (94.7)</b>	<b>54 (2.0%)</b>	<b>11.1%</b>	

\*Mifepristone oral 200 mg followed in 24-48 hour range with misoprostol buccal 800 mcg.

\*\*Boersma study reported the interval from 50-63 days without further breakdown.

Source: Data from published studies.

<sup>48</sup> 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.

<sup>49</sup> Bracken H ,Dabash R, Tsertsvadze G et al. A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial. *Contraception* 2014;89(3):181-6.



Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

**Reviewer comments:**

**Although the Chong and Bracken studies do not use the exact proposed dosing regimen, it is felt that their efficacy results are relevant because both used a lower dose of misoprostol, which, if anything, would have been expected to provide lower efficacy.**

**After careful review of the above eight studies, we find the following results. A combined total of 3,072 women were treated at 57-63 days of gestation, with 2,730 (88.9%) providing outcome data. Of these women, 2,585 (94.7%) had a complete medical abortion (pregnancy termination without any surgical intervention), and 54 (2.0%) had ongoing pregnancies. This successful treatment rate is better (94.7% compared to 92.1%) than the rate in the data on which the 2000 FDA Mifeprax approval was based. The data are sufficient and acceptable for extending the approval of Mifeprax up to at least 63 days gestation.**

**The numbers here do not exactly match the results shown in the efficacy table for 57-63 gestational days that are in Section 14 CLINICAL STUDIES in the new approved label, which is limited to studies using the identical dosing regimen to that proposed in this supplement. The number of evaluable women here is higher because the Chong and Bracken data are included, as noted above in the comment. The label, however, states the same conclusion of a 94.7% complete medical abortion rate and a 2% ongoing pregnancy rate.**

**Data for 64-70 days gestation are found in the next table.**

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

**Table 7: MAB Efficacy Outcome 64-70 Days Gestation**

Study	Enrolled N	Followed N	Success N (%)	Ongoing Pregnancy N (%)	Lost to Follow up %	Comment
Winikoff <sup>19</sup> 2012	350	304	282 (92.8)	9 (3.0)	13.1	*Proposed dosing
Sanhueza <sup>48</sup> 2015	150	147	134 (91.2)	5 (3.4)	2.0	* Proposed dosing
Boersma <sup>22</sup> 2011†	26	26	25 (96.2)	1 (3.8)	0	Proposed dosing @ 24-36 hr @ home
Pena <sup>44</sup> 2014	2	2	2 (100)	0 (0)	0	* Proposed dosing
Chong <sup>40</sup> 2012 RCT	1	1	1 (100)	0 (0)	0	* Proposed dosing @ 36-48 hr
	6	6	6 (100)	0 (0)	0	400 mcg buccal
<sup>Y</sup> Gouk <sup>47</sup> 1999 UK-misoprostol in hospital	127	127	120 (94.5)	7 (5.5)	0	800 mcg vaginal @ 36-48 hr
Bracken <sup>49</sup> 2014	325	321	295 (91.9)	7 (2.2)	1.2	400 mcg sublingual @ 24-48 hr
<b>TOTAL</b>	<b>987</b>	<b>934</b>	<b>865 (92.6)</b>	<b>29/934 (3.1)</b>	<b>53/987 (5.4)</b>	

\*Mifepristone oral 200 mg followed in 24-48 hour range with misoprostol buccal 800 mcg.

<sup>Y</sup>The Gouk study in 1996-97 included 253 women at 63-83 days gestation (Weeks 10-12).

Source: Table modified with data from published studies. See Abbas D et al. Contraception [MAB through 70 days gestation] 92 (2015):197-199.

**Reviewer comments:**

Use of the Chong and Bracken data is discussed above. Although the Gouk regimen used a different route of administration for misoprostol, the effectiveness of the vaginal route appears to be similar to that of the buccal route; therefore, these data are considered relevant. Data on sublingual administration of misoprostol may be less generalizable due to the different pharmacokinetic (PK) profile and higher AE frequency compared to buccal

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

**administration. Also, see Section 4.4.3 Pharmacokinetics and the Cross Discipline Team Leader review.**

**The abortion success rates shown above from seven studies are comparable to (and in several studies, greater than) the success rates for medical abortion in the initial 2000 decision for Mifeprex up to 49 days gestation. The proportion of subjects with complete success without any medical or surgical intervention in the US pivotal trial that supported the original approval was 92.1%, as shown in Table 5, in 827 women encompassing all gestational weeks up to 49 days. The data in the above two tables include 3,072 women treated at 57-63 days gestation and 987 women at 64-70 days gestation. We believe that this comprises a sufficient number of women in each gestational week upon which to make a clinical decision, and that the overall 94.7% and 92.6% success rates are acceptable for approval.**

**The data here clearly establish the efficacy of medical abortion with mifepristone and misoprostol through 70 days gestation. At least two Gynuity Health studies of outpatient medical abortion through 70 days are ongoing, so more information from clinical studies will be available in the future.**

**It is also worth noting that in November 2015, the National Medical Committee of PFA approved medical abortion through 70 days, so this is currently their standard of care.**

**Reviewer's Final Recommendation:**

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

**6.1.8 At-home Administration of Misoprostol**

For the majority of women, the most significant cramping and bleeding will occur within 2-24 hours after taking misoprostol. Requiring women to take misoprostol in the office necessitates another visit and can interfere with the woman's ability to make reasonable plans for the expected bleeding and cramping. With the option to take misoprostol at home the woman can:

- **Plan to experience cramping and bleeding at a safe and convenient time when support is available**
- **Minimize loss of income (for childcare or missed days of work)**
- **Experience improved comfort, satisfaction and privacy**

Data (graph below) from Winikoff (2012)<sup>19</sup> shows the time in hours to complete expulsion of the pregnancy after misoprostol administration for gestations at 57-63 and 64-70 days. Within about 5 hours after misoprostol dosing, 50-60% of the MABs are complete.



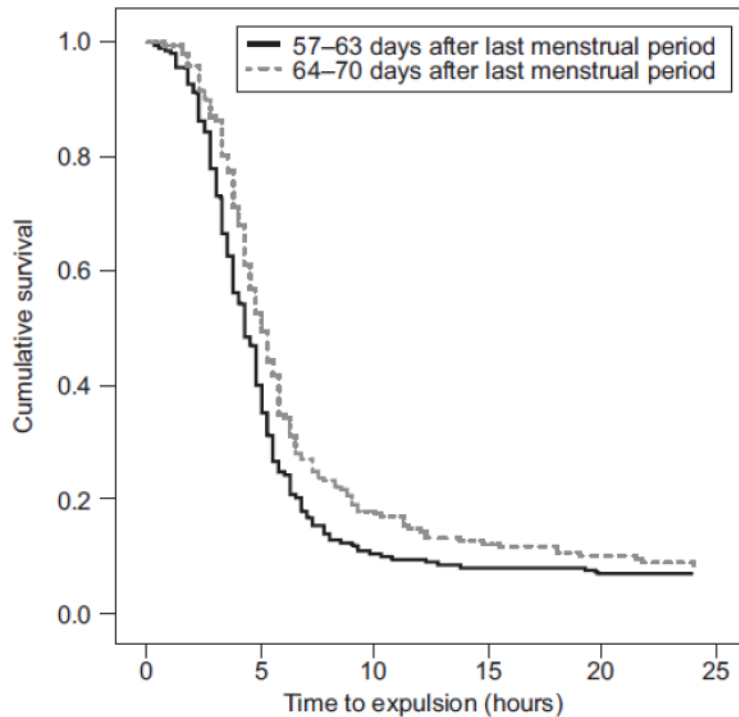
## Clinical Review

(b) (6)

and

(b) (6)

NDA 020687/S-020- Mifeprax



Many studies have recorded data on home use in the US and elsewhere and “demonstrated that 87-97% of women find home use of misoprostol acceptable. Home use of misoprostol is now standard in the US.”<sup>50</sup> The 2009-10 Swica comparative study focused on the option to take both mifepristone and misoprostol at home after being counseled at the office/clinic. There was no significant difference in either efficacy or safety for the 139 women (46%) who took both medications at home compared to 161 women who took mifepristone in the office and misoprostol at home.

Table 8 that follows is a list of studies where data are available on home use of misoprostol and the specific efficacy findings.

<sup>50</sup> Swica Y, et al. Acceptability of home use of mifepristone for medical abortion. *Contraception* 2013;88:122-127.

## Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex**Table 8: Misoprostol Self-administration at Home**

Study	Evaluable N	Misoprostol at home	Success	Comment
<b>US Studies</b>				
Gatter 2015 <sup>13</sup> US	13,373	All subjects at 24-48 hr	97.7%	Through 63 days; buccal miso 800 mcg
Winikoff 2008 <sup>23</sup> US	421	All subjects at 24-36 hr	96.2%	Through 63 days; buccal miso 800 mcg
Winikoff 2012 <sup>19</sup> US	629	All subjects at 24-48 hr	93.5% (Wk 9) 92.8% (Wk 10)	<b>Week 9 v Week 10;</b> buccal miso 800 mcg
Swica 2013 <sup>50</sup> US	301	All subjects at 6-48 hr	96.7 %- home mife 95.6%- clinic mife	Through 63 days; 800 mcg miso
<b>Foreign Studies</b>				
Louie 2014 <sup>14</sup> Azerbaijan	863	794 (92%) at home at 24-48 hr	97%	Through 63 days; buccal miso 800 mcg
Pena 2014 <sup>44</sup> Mexico	1,000	All subjects at 24-48 hr	97.3%	Through 63 days; buccal miso 800 mcg
Bracken 2014 <sup>49</sup> 4 countries	703 (382 v 321)	543 (77%) took miso at 24-48 hr	94.8% (Wk 9) v 91.9% (Wk 10)	<b>Week* 9 v Week 10</b> 400 mcg sublingual miso used
Boersma 2011 <sup>22</sup> Curacao	307	All subjects at 24-36 hr	97.7%	Through 70 days (Wk 10); <b>GP care;</b> buccal miso 800 mcg;
Chong 2012 <sup>40</sup> 400 v 800 buccal	1115 (559 v 563 were enrolled)	851 (76%) at 36-48 hr	96.8% with <u>home</u> miso; 95.1% with clinic miso	Through 63 days; *DB, RCT in Vietnam and Georgia
Goldstone 2012 <sup>20</sup> Australia:	11,155	All subjects at 24-48 hr	96.5%	Through 63 days; <b>buccal miso 800 mcg</b>
Sanhueza 2015 <sup>48</sup>	896	All subjects at 24-48 hr	93.3	<b>Through 70 days (Wk 10)</b>
<b>TOTAL</b>	<b>30,763</b>	<b>30,210 (98.2%)</b>	<b>92%-97.7%</b>	<b>Different gestations, and regimens</b>

\*DB, RCT: double-blind, randomized clinical trial.

Source: FDA clinical reviewer table.

**Reviewer comments:**

The above table with data for home administration of misoprostol for 30,763 women in the US and other countries shows a success rate ranging from 91.9 to

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

**97.7%. The two largest studies (Gatter and Goldstone) pooled showed 97% success using the new proposed dosing regimen with home use of buccal misoprostol. The lowest success rate above of 91.9% in the Bracken study is still supportive for approval and does not differ significantly from results with misoprostol taken in the clinic/office.**

**Of note is that 4 of the above studies provided data on home use of misoprostol through 70 days gestation.**

**Home use of misoprostol has been evaluated as part of the proposed protocol in studies including well over 30,000 patients, as well as in studies of home use of both mifepristone and misoprostol. The Raymond (2013) review<sup>18</sup> of early MAB with mifepristone 200 mg and misoprostol (different doses and routes of administration), analyzed 87 trials with 47,283 treated women up to 63 days gestation. The article concludes: “We found no evidence that allowing women to take the misoprostol at home increased the rate of abortion failure or serious complications.” It is also notable that the NAF and ACOG guidances encourage home administration of misoprostol and it has been standard protocol for most PPFA clinics for since 2005.**

**While we do not have age-specific efficacy data for adolescents who took misoprostol at home, it is evident that many adolescents did take buccal misoprostol at home. In the Goldstone 2012 study, there were eight 14 year olds and 931 women ages 15-19 who took misoprostol at home. In the Gatter 2015 study, there were 24 adolescents age 11-14, 82 age 15, 216 age 16, and 435 age 17 who took misoprostol at home. The overall efficacy in these two large studies was excellent, as previously noted.**

**Reviewer’s Final Recommendation:**

**There is no medical rationale against permitting the woman to be given the misoprostol on the day of the initial clinic/office visit and self-administer it at a convenient time in the next 24-48 hours at home. This would avoid another visit and the time, transportation, loss of work, inconvenience, etc. that such a visit would involve. Furthermore, given the fact that 22-38% of women abort within 3 hours and 50-60% within 5 hours of buccal misoprostol<sup>19</sup>, it is preferable for the woman to be in a convenient, safe place (home or at a support person’s location) for the expected uterine cramping and vaginal bleeding to occur. The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol shows acceptable efficacy when misoprostol is self-administered at home.**

**6.1.9 Use of a Repeat Dose of Misoprostol if Needed**

**Several studies using buccal misoprostol allowed the option of repeat misoprostol at follow-up one week after mifepristone for persistent gestational sac; however, only a few**



(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

studies report specific outcomes. The Chen and Creinin 2015 review<sup>12</sup> of mifepristone with buccal misoprostol for MAB reported on four studies. Chong (2012)<sup>40</sup> provided additional information from 1,122 women. In the study protocols, women with an ongoing pregnancy at follow-up were recommended to undergo uterine suction curettage, whereas women who had retained products of conception were given the options of expectant management, suction curettage/aspiration, or a second dose of misoprostol. Limited additional data were provided by Gatter (2015)<sup>13</sup>: data on the use of a repeat dose of misoprostol were available from a subset of 7,335 women, of whom 87 (1.2%) received a repeat dose. Efficacy results, however, are not stated in the Gatter article, so this study is not included in Table 9, which highlights success rates after a repeat dose of misoprostol in seven published articles that included this specific outcome.

**Table 9: Success with a Repeat Dose of Misoprostol - Incomplete MAB**

Study/Country	Total N	Mife-Miso Interval (hrs)	Took 2 <sup>nd</sup> Dose	Success with 2 <sup>nd</sup> dose N (%)	Comment
*Raghavan 2010 <sup>51</sup> Moldova	277	24	2	2 (100)	Buccal Miso 400
*Winikoff 2008 <sup>23</sup> US	421	24-36	14	13 (93)	Buccal Miso 800
*Winikoff 2012 <sup>19</sup> US	629	24-48	<sup>Y</sup> 20	<sup>Y</sup> Wk 9- 11 (91) Wk 10: 9 (67)	Week 9 v. Week 10: Buccal Miso 800
*Louie 2014 <sup>14</sup> Azerbaijan	863	24-48	16	16 (100)	Buccal Miso 800
Chong 2012 <sup>40</sup> Georgia, Vietnam	1122	36-48	47	43 (92)	Buccal Miso 400 and 800 mcg
Boersma 2011 <sup>22</sup> Curacao	307	24-36 hr	5	4 (80)	GP care; Buccal Miso 800 at home
Bracken 2014 <sup>49</sup> 4 countries	703	24-48 hr	33	29 (88)	Sublingual Miso 400
<b>TOTALS</b>	<b>4,018</b>	<b>--</b>	<b>137 (3.4%)</b>	<b>123 (90%)</b>	

\*These 4 studies are in Table 4 of the Chen and Creinin 2015 review article.

<sup>Y</sup>These data are directly from the Winikoff article; the Chen and Creinin review had incorrect data.

Source: table modified by FDA reviewer from Chen and Creinin 2015 article and 3 other studies.

<sup>51</sup> Raghavan S, et al. Comparison of 400 mcg buccal and 400 mcg sublingual misoprostol after mifepristone medical abortion through 63 days' LMP: a randomized controlled trial. Contraception 2010; 82:513-9.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex**Reviewer's comment:**

The completion success rates shown above are high. While only 3.4% of the women took a second misoprostol dose, 90% of these women avoided a surgical procedure to complete their termination. We believe the option of a repeat dose of misoprostol is acceptable and safe in the case that complete expulsion has not occurred after initial dosing (provided that the pregnancy is not still ongoing): it offers a choice for the healthcare provider and the patient on how to manage an incomplete expulsion (retained products of conception) following the initial treatment. As noted above, the other options are expectant management, suction aspiration in the office, or a surgical D&C in the operating room. It is also of note that it is standard protocol in many US clinics to offer the choice of a repeat misoprostol dose, especially for women with an incomplete termination (retained tissue/clots or a documented non-viable pregnancy). A second dose of misoprostol is generally not offered in the case of a documented ongoing pregnancy following use of mifepristone and misoprostol.

**Reviewer's Final Recommendation:**

Use of a repeat dose of misoprostol may be offered when using the new dosing regimen if the pregnancy has ended, but the expulsion is incomplete.

**6.1.10 Physician v Other Healthcare Provider Treatment**

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies took place in varying settings (urban, rural, international, low resource). The efficacy results are as follows:

- Olavarietta<sup>85</sup> demonstrated efficacy of 97.9% when the MAB was provided by nurses as compared with 98.4% with physicians
- Kopp Kallner<sup>84</sup> showed efficacy of 99% with certified nurse midwives versus 97.4% with physicians
- Warriner<sup>52</sup> demonstrated efficacy of 97.4% with nurses versus 96.3% with physicians
- Puri<sup>83</sup> showed efficacy of 96.8% compared with 97.4% in the "standard care" group

**Reviewer comment:**

The above findings for MAB efficacy from 5 studies clearly demonstrates that efficacy is the same with non-physician providers compared to physicians or the

---

<sup>52</sup> 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.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

“standard care” treatment.

### 6.1.11 Follow-up Timing and Method

Concerning follow-up timing and method, follow-up within the 7-14 day interval after mifepristone administration is universally recommended; however, follow-up does not necessarily need to be done as currently labeled “in the clinic or healthcare provider’s office 14 days after Mifeprex administration.”

One strong argument for flexibility in follow-up timing, location and method after the administration of Mifeprex and misoprostol is to avoid placing an undue burden on either the provider or the patient, while maintaining the ability to identify incomplete terminations. The currently approved labeling specifies three visits (two for dosing, one for follow-up) at fairly rigid times that are often not practical, convenient or necessary.

Several articles were submitted by the Applicant to support flexible follow-up. The most noteworthy article is the 2013 Raymond review<sup>18</sup> of over 45,000 MABs using 200 mg oral mifepristone that concluded: “we observed no significant association between abortion failure rates and the timing of the follow-up evaluation.” This topic is discussed thoroughly in the Section Submission-Specific Primary Safety Concerns.

#### **Reviewer comment:**

**Follow-up during the 7-14 day window after the administration of mifepristone is necessary to determine that the termination was successful and the woman is in good health. If for some reason the follow-up contact is not made (the woman is “lost to follow-up”), the clinical guidelines of NAF state that “all attempts to contact the patient (phone calls and letters) must be documented in the patient’s medical record.” This guideline emphasizes the importance of follow-up but accepts the fact that women are sometimes lost to follow-up and there is no mechanism that can guarantee 100% follow-up in the normal clinical setting.**

#### **Reviewer’s Final Recommendation:**

**Follow-up after taking Mifeprex and misoprostol is necessary. The exact timing and method should be flexible and determined jointly by the healthcare provider and the individual woman being treated, and should follow the standard guidelines for the office/clinic where the Mifeprex is being dispensed. Fortunately, there are several choices/methods of follow-up that can be used and it appears that no single option is superior to the others. The woman should always have the option to be seen at the office/clinic.**

### 6.1.12 Subpopulations

#### **Parity**

The Raymond (2013) review article<sup>18</sup> had 74 trials with parity data for ~ 32,000 women. In 34 trials whose study populations comprised > 50% nulliparous women, the MAB success rate was 96.4%; in 40 trials with ≤ 50% nulliparous women, the success rate was 94.9%. This suggests that women who have not had a previous term pregnancy



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

delivery have a slightly higher early MAB success rate. These data are not definitive, however, because such factors as the dosing regimen, route of administration, and gestational age could also influence the success rates.

### **Previous abortion**

One study<sup>26</sup> found that success rates are slightly better in women who have not had a previous abortion. Prior abortion, however, did not appear to be an important risk factor for abortion failure or success (Raymond<sup>18</sup>).

### **Race**

There does not appear to be any efficacy difference based on race. Results are reported in studies enrolling a large number of women. Gatter (2015)<sup>13</sup> had five racial/ethnicity groups among over 13,000 women at the PPFA centers in the Los Angeles area; the success rates ranged from a low of 97.2% (African-American) to a high of 97.8% (White, Asian and Other), which is not clinically or statistically significant.

### **Adolescents v. Older Women**

There are at least three articles that support the efficacy of MAB in adolescents; each study used the same definition of success as the need for no further medical or surgical intervention:

- Phelps et al. 2001<sup>53</sup> conducted a pilot study in 28 adolescents aged 14-17, at  $\leq 56$  days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. All 28 had complete medical terminations without complications or surgical intervention. Five adolescents did not require any misoprostol.
- Niinimaki et al. April 2011:<sup>54</sup> Finnish Registry from 2000-06 comparing rates of AEs in adolescents and adult women with MAB at  $\leq 20$  weeks gestation, which included 3,024 women < age 18 and 24,006 women age 18 or older. By gestational age, 2,424 adolescents were < 64 days gestation and 139 were within 64-84 days gestation. The specific dose regimens are not stated and may have varied according to the gestational ages. The odds ratio for an incomplete abortion for adolescents under age 18 compared to the women  $\geq$  age 18 was 0.69, meaning that the younger women had a lower rate of incomplete abortions.
- Gatter, Cleland and Nucatola (2015):<sup>13</sup> US data using the proposed regimen of mifepristone 200 mg and misoprostol 800 mcg buccally through 63 days included 283 women aged 17 years and 322 under age 17 (see Table 10). The 605 women under age 18 had a 98.7% success rate while the 6,674 18-24 year olds had a 98.1% success rate. The four older age groups had success rates that ranged from 96.5 to 97.5% without any need for a surgical procedure and additional treatment. In

<sup>53</sup> Phelps RH, et al. Mifepristone abortion in minors. *Contraception* 2001;64:339-343.

<sup>54</sup> 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.

## Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprax

the pediatric population, there were no cases requiring transfusion, hospitalization or treatment for severe infection.

The table below shows the age distribution from the Gatter study. There were 24 adolescents between ages 11-14, 82 adolescents age 15, and 216 age 16 totaling 322 adolescents. As noted, 283 adolescents were age 17.

**Table 10: MAB Success by Age Group**

Age Group (years)	Total N Success (%)	Comment
< 18	605 (98.7)	322 were age 11-16 283 were age 17
18-24	6684 (98.1)	The age distribution here is representative of other US data on MAB - largest group is age 18-24 followed by age 25-29
25-29	3317 (97.5)	
30-34	1613 (96.5)	
35-39	855 (97.0)	
40+	299 (97.3)	
<b>TOTAL</b>	<b>13,373</b> <b>97.7% overall success</b>	

Source: Data from Gatter 2015 review.

**Reviewer comments:**

Data from 3,657 adolescents under age 18 in the above three studies shows a MAB success rate that is consistently equal to or higher than that found in the women older than age 17. It is interesting that five (18%) of the adolescents in the Phelps study did not even need misoprostol. The percentage of women not needing any misoprostol is generally much lower, perhaps 1-3%, in other early MAB studies. From the articles reviewed, efficacy of early MAB in the adolescent population is not a concern.

**Additional adolescent data were reported in the Goldstone 2012 study<sup>20</sup>**, where there were eight 14 year olds and 931 women ages 15-19 who took misoprostol at home for a MAB up to 63 days gestation. Efficacy and safety data by age groups were not reported in the article.

**6.1.13 Analysis of Clinical Information Relevant to Dosing Recommendations**

As noted in some of the reviewer comments and tables, there is evidence that lower doses of misoprostol (400 mcg), other ROAs (vaginal and sublingual), inclusion of more advanced gestational ages, and different dosing intervals between mifepristone and misoprostol have shown acceptable efficacy and safety results. However, for the purposes of this NDA review, our final recommendations are focused on the dosing regimen and other requests specifically made by the Applicant.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

#### **6.1.14 Discussion of Persistence of Efficacy and/or Tolerance Effects**

There is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. Return to fertility is well-documented: in the Patient Counseling Information section, the labeling states “inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses” and “inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before she resumes sexual intercourse.”

#### **6.1.15 Additional Efficacy Issues/Analyses**

The Applicant has requested that revised labeling provide only for the new proposed regimen and that the original approved regimen be deleted.

#### **Reviewer Final Recommendation:**

**While there are no safety or efficacy reasons that would lead us to withdraw approval of the currently labeled dosing regimen, we concur that it may be deleted from labeling because very few providers currently use it, and inclusion of two options for dosing could be confusing. Of note, PPFA and NAF guidelines have used mifepristone 200 mg oral and misoprostol 800 mcg (initially given vaginally and now buccally) since 2001.**

## **7 Review of Safety**

### **Safety Summary**

- Medical abortion with the new proposed regimen of Mifeprex 200 mg followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation is safe. Major adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are reported rarely in the literature on over 30,000 patients. The rates, when noted, are exceedingly rare, generally far below 0.1% for any individual adverse event. The number of postmarketing deaths associated with Mifeprex pharmacovigilance is very low. Non-vaginal routes of administration of misoprostol have increased and since the *C. sordellii* deaths associated with vaginal misoprostol, there have been no *C. sordellii* deaths. Given that the numbers of these adverse events appear to be stable or decreased over time, it is likely that these serious adverse events will remain acceptably low.
- Common adverse events associated with medical abortion occur at varying but acceptable rates.
- There are scarce cases of uterine rupture associated with early medical abortion. Medical abortion using mifepristone with or without misoprostol in the first trimester is safe from this perspective.



## Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

- There does appear to be an association between angioedema and mifepristone administration. The risks of anaphylaxis and angioedema should be included in the labeling for Mifeprex and there should be continued pharmacovigilance for anaphylaxis.
- Home use of misoprostol has been evaluated as part of the proposed dosing regimen in studies including well over 30,000 patients, demonstrating an acceptable safety profile, with rates of adverse events equal to or lower than those with the approved regimen requiring in-office dispensing of misoprostol. Home use of misoprostol can increase patient convenience, autonomy and privacy without increased burden on the healthcare system.
- In the articles about repeat misoprostol after mifepristone administration, there is little information provided about safety. The need for a second dose is a relatively uncommon occurrence. In studies of medical abortion using misoprostol alone, using two or more doses as compared to one dose of misoprostol does increase the risk of the common adverse event of diarrhea. There are a very few reports of uterine rupture with multiple doses of misoprostol, in almost all cases in women with prior uterine surgery, such as a cesarean section.
- The Applicant demonstrates that alternatives to in-clinic follow-up, including standardized questions, telephone follow-up, and use of low and high sensitivity urine pregnancy tests, serum pregnancy tests, and ultrasound are effective and safe. Loss-to-follow-up rates do not exceed those of in-clinic follow-up. This option can increase flexibility and accessibility of medical abortion for women.
- Medical abortion in adolescents appears to be at least as safe, if not safer, as in adult women. These data support the safety of Mifeprex in adolescents and satisfy requirements for PREA. No information on safety or efficacy if used in premenarchal girls is required, as the medication is not indicated in that subset of the pediatric population.
- Midlevel providers in the United States, such as nurse practitioners, nurse midwives and physician assistants currently provide family planning services and abortion care, including medical abortion care, under the supervision of physicians. In light of the REMS requirements, midlevel providers who are currently practicing abortion care are doing so under the supervision of physicians. Therefore, facilities that employ midlevel providers already have an infrastructure in place for consultation and referral if, as required under the REMS, a prescriber is unable to provide additional care, including surgical management if needed.
- It is appropriate to modify the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." FDA has received

## Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

such reports for 15 years, and it has determined that the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely. For this reason, FDA does not believe ongoing reporting of all of the specified adverse events is warranted. The proposed Prescriber's Agreement Form (to replace the Prescriber's Agreement) will continue to require that qualified healthcare providers report any deaths. The Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience.

- Upon review of historical documents and of current guidelines for REMS materials, the phrase "under Federal law" can be removed from the Prescribers' Agreement. We concur with (b) (6) review of the REMS document.
- The revised Indication Statement should read:

"Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation." Safe use of Mifeprex would be enhanced when other information necessary to describe appropriate use (i.e., the need to use Mifeprex in a combined regimen with misoprostol and the gestational age for use) is included in the Indication Statement. This would be consistent with current FDA thinking (e.g., the internal Label Review Tool) which states that the indication and use statement should include "Information if drug is to be used only in conjunction with another therapy."

## 7.1 Methods

The assessment of the clinical safety of Mifeprex through 70 days gestation is based on the Applicant's submission of numerous articles from the peer-reviewed medical literature. The various studies have different designs, inclusion criteria, dosing regimens and endpoints for safety and efficacy. For the evaluation of safety, this reviewer focused on the studies that evaluated the proposed dosing regimen. All the articles used for this review can be found in the extensive list of references in Section 9.6 at the end of this review.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The reviewer evaluated safety based on the studies that focused on the proposed dosing regimen, specifically Mifeprex 200 mg followed by misoprostol 800 mcg buccally 24-48 hours later, as listed in Table 11 below. Supportive data from studies that have less specific numerical data or studies that included other regimens, specifically with different routes of administration of misoprostol (vaginal, oral, sublingual) are not included in this portion of the review, but are discussed in Sections Major Safety Results and Supportive Safety Results. Table 11 lists the studies referenced in these discussions.

## Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

**Table 11: Studies Used to Evaluate Safety**

Study	
USA	International
Gatter 2015 <sup>13</sup> , retrospective	Ngoc 2014 <sup>16</sup> , Vietnam, prospective
Ireland 2015 <sup>15</sup> , retrospective	Goldstone 2012 <sup>20</sup> , Australia, retrospective
Chong 2015 <sup>17</sup> , prospective single-arm	Boersma 2011 <sup>22</sup> , Curacao, prospective
Winikoff 2012 <sup>19</sup> , prospective	
Grossman 2011 <sup>36</sup> , prospective	
Winikoff 2008 <sup>23</sup> , prospective RCT	
Creinin 2007 <sup>25</sup> , prospective	
Middleton 2005 <sup>24</sup> , prospective	

Source: NDA clinical reviewer table.

### 7.1.2 Categorization of Adverse Events

For the purposes of this review, adverse events categorized as serious include death; hospitalization; infection, including severe infection requiring hospitalization; bleeding requiring transfusion; and ectopic pregnancy. Other non-serious adverse events include: nausea, vomiting, diarrhea, fever, bleeding and cramping.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The data are not pooled across studies as the study designs are quite different. The incidence of individual adverse events is noted for each study, and can be used to provide an estimated range.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Per the Applicant, there have been approximately 2.5 million US uses of Mifeprex by US women since its approval in 2000. If evaluation is limited to the studies listed in Table 11 focusing specifically on the proposed new dosing regimen, exposure for this safety analysis is based on well over 30,000 patients. The exact number cannot be determined because two retrospective studies (Gatter<sup>13</sup> and Ireland<sup>15</sup>) are likely based on overlapping cohorts of patients from Planned Parenthood clinics in Los Angeles. There are likely some differences in the demographic data for the different studies; therefore, the descriptions are separated into US and international data. However, it is doubtful



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

that demographic differences such as race or ethnicity are clinically meaningful in relation to the safety and efficacy of medical abortion. The data do include adolescents exposed to Mifeprax; information on safety in this population is discussed in Section 7.4.5.

### **7.2.2 Explorations for Dose Response**

NA for this review.

### **7.2.3 Special Animal and/or In Vitro Testing**

NA for this review.

### **7.2.4 Routine Clinical Testing**

From this reviewer's assessment of the literature, no routine clinical testing is needed to evaluate the proposed changes to the Mifeprax labeling.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

NA for this review.

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

Please see Important Safety Issues with Consideration to Related Drugs for discussion of potential adverse events for drugs in this class.

## **7.3 Major Safety Results**

### **7.3.1 Deaths**

Deaths are rare with medical abortion. Most of the articles provided did not specifically report on deaths with medical abortion. Among the seven US studies, only one reported on deaths (Grossman, 2011<sup>36</sup>) and noted zero deaths among 578 subjects. Among the three international studies, only one<sup>20</sup> reported on deaths. In this retrospective review of 13,345 medical abortions with the proposed regimen, the authors reported only one death, yielding a rate of 0.007%. More information on deaths associated with medical abortion is found in Section 8 Postmarket Experience.

### **7.3.2 Nonfatal Serious Adverse Events**

The nonfatal serious adverse events typically discussed in the literature are hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. See narratives below and Table 12, Table 13, and Table 14 for details.

#### Hospitalization data:

Most articles do not report hospitalization data. In the US studies, 19 patients were reported as being hospitalized out of a total of 16,696 subjects. The overall rates range

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

from 0.003-1.1%. Only three articles separated out hospitalizations by gestational age. In Gatter 2015<sup>13</sup>, there were 3/8495 hospitalizations among women  $\leq$  49 days, 3/3142 among women at 50-56 days gestation and none among women at 57-63 days. In Winikoff 2012<sup>19</sup>, there were only two hospitalizations, both among women at 57-63 days, and none in the 64-70 days gestation group. In Creinin<sup>25</sup> two of six total hospitalizations were in the 50-56 days group and two in the 57-63 days group. The two remaining hospitalizations in that study were unrelated to study drug and gestational age information was not provided for these two cases. There were none among women at 64-70 days gestation. See Table 12 below.

Among the international studies, only 3 of 15,109 women were hospitalized, with rates from 0.07-0.6%. These rates were not separated out by gestational age. See Table 12.

APPEARS THIS WAY ON ORIGINAL

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprax

**Table 12: Hospitalizations by Gestational Age**

Study	Design	Subjects (N)	Hospitalizations by gestational age [Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
<b>USA</b>							
Gatter 2015 <sup>13</sup>	retrospective	13,373	6‡ (0.04%)	N=8945 3/8945 (0.03%)	N=3142 (0.1%)	N=1286 0	N/A
Chong 2015 <sup>17</sup>	prospective	400	2 (0.5%)	NR*	NR	NR	N/A
Winikoff 2012 <sup>19</sup>	prospective	729	2 (0.27%)	N/A	N/A	N=325 2 (0.61%) <sup>^</sup>	N=304 0%
Grossman 2011 <sup>36</sup>	prospective	578	0	N=283 0%	N=103 0%	N=63 0%	N/A
Winikoff 2008 <sup>23</sup>	prospective	421	3(0.71%)	N=213 NR	N=93 NR	N= 115 NR	N/A
Creinin 2007 <sup>25</sup>	prospective	546	6 (1.1%)§	N=229 0%	N=172 2 (1.16%)§	N=145 2 (1.38%)§	NA
Middleton 2005 <sup>24</sup>	prospective	223	NR	NR	NR	N/A	N/A
<b>International</b>							
Ngoc 2014 <sup>16</sup> Vietnam	prospective	1433	1 (0.07%)	NR	NR	NR	N/A
Goldstone 2012 <sup>20</sup> Australia	retrospective	13,345	NR	N=11,855 NR	N= 1441 NR	N=49 NR	N/A
Boersma 2011 <sup>22</sup> Curacao	prospective	331	2/331 (0.6%)	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

\* NR= not reported

‡numbers of hospitalizations for Gatter study includes those for bleeding and infection in subsequent tables.

<sup>^</sup> includes woman with sepsis noted in Table 13, and one woman with chronic pancreatitis, recurrent.

§includes subjects receiving transfusions noted in Table 14.

**Source: NDA clinical reviewer table.**

Serious infection:

Infections requiring hospitalization or IV antibiotics were rare in the studies. Only three US studies captured this information, with rates ranging from 0-0.015%. Two studies separated this information out by gestational age. In Gatter 2015<sup>13</sup>, the two serious infections were in women ≤ 49 days gestation. There were no serious infections in



(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

women at 50-56 or 57-63 days gestation. In Winikoff 2012<sup>19</sup>, there was one serious infection in a woman at 57-63 days and none in women at 64-70 days. See Table 13.

Among the international studies, there were five women hospitalized with rates from 0.03-0.07%. This information was not broken down by gestational age. See Table 13.

**Table 13: Serious Infection by Gestational Age**

Study	Design	Subjects (N)	Serious Infection by gestational age {Total N in subgroup, rate (%)}				
			All Gestational Ages (Overall/ not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
<b>USA</b>							
Gatter 2015 <sup>13</sup>	retrospective	13,373	2 (0.015%)	N= 8945 2 (0.022%)	N= 3142 0%	N=1286 0%	N/A
Chong 2015 <sup>17</sup>	prospective	400	NR*	NR	NR	NR	N/A
Winikoff 2012 <sup>19</sup>	prospective	729	1 (0.014%)	N/A	N/A	N=325 1 (0.31%)	N=304 0%
Grossman 2011 <sup>36</sup>	prospective	578	NR	N=283 NR	N=103 NR	N=63 NR	N/A
Winikoff 2008 <sup>23</sup>	prospective	421	NR	N=213 NR	N=93 NR	N=115 NR	N/A
Creinin 2007 <sup>25</sup>	prospective	546	0	N=229 0%	N=172 0%	N=145 0%	N/A
Middleton 2005 <sup>24</sup>	prospective	223	NR	NR	NR	N/A	N/A
<b>International</b>							
Ngoc 2014 <sup>16</sup> Vietnam	prospective	1433	1 (0.07%)	NR	NR	NR	N/A
Goldstone 2012 <sup>20</sup> Australia	retrospective	13,345	4 (0.03%)	N=11,855 NR	N=1441 NR	N=49 NR	N/A
Boersma 2011 <sup>22</sup> Curacao	prospective	331	NR	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

\* NR= not reported

Source: NDA clinical reviewer table.

Transfusion data:

With regard to bleeding requiring transfusion, five of the seven US studies included this information as shown in Table 14. The rates of transfusion range from 0.03-0.7%.

Three of the studies provided a breakdown by gestational age. In Gatter 2015<sup>13</sup>, there were the following: one woman in the ≤ 49 days group, three in the 50-56 days and zero in the 57-63 days group. In Winikoff 2012<sup>19</sup>, there were: two in the 57-63 days group

## Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

and 1 in the 64-70 days group. In Creinin 2007<sup>25</sup>, there were two women transfused each in the 50-56 days and 57-63 days. Only one international study<sup>20</sup> (Goldstone 2012) reported on transfusions and 11/13,345 women or 0.08% required transfusion.

**Table 14: Transfusion by Gestational Age**

Study	Design	Subjects (N)	Bleeding Requiring Blood Transfusion by gestational age [Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
<b>USA</b>							
Gatter 2015 <sup>13</sup>	retrospective	13,373	4 (0.03%)	N=8945 1 (0.01%)	N=3142 3 (0.1%)	N=1286 0	N/A
Chong 2015 <sup>17</sup>	prospective	400	NR	NR	NR	NR	N/A
Winikoff 2012 <sup>19</sup>	prospective	729	3 (0.41%)	N/A	N/A	N=325 2 (0.53%)	N=304 1 (0.29%)
Grossman 2011 <sup>36</sup>	prospective	578	1 (0.17%)	N=283 NR	N=103 NR	N=63 NR	N/A
Winikoff 2008 <sup>23</sup>	prospective	421	NR	N=213 NR	N=93 NR	N=115 NR	N/A
Creinin 2007 <sup>25</sup>	prospective	546	4(0.7%)	N=229 0	N=172 2 (0.36%)	N=145 2 (0.36%)	N/A
Middleton 2005 <sup>24</sup>	prospective	223	1 (0.45%)	NR	NR	N/A	N/A
<b>International</b>							
Ngoc 2014 <sup>16</sup> Vietnam	prospective	1433	NR	NR	NR	NR	N/A
Goldstone 2012 <sup>20</sup> Australia	retrospective	13,345	11 (0.08%)	N=11,855 NR	N=1441 NR	N=49 NR	N/A
Boersma 2011 <sup>22</sup> Curacao	prospective	331	NR	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

\*NR= not reported

Source: NDA clinical reviewer table.

Ectopic pregnancy:

Ectopic pregnancies were rarely reported in the supporting literature submitted with this efficacy supplement. Only one ectopic pregnancy was reported among 847 patients (0.12%) in Winikoff 2008<sup>23</sup>.

Several studies also included less detailed, though still useful, information on adverse events. Ireland et al<sup>15</sup> conducted a retrospective review of 30,146 women undergoing

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

medical or surgical abortion at  $\leq$  63 days gestation at Planned Parenthood clinics in Los Angeles between November 1, 2010 and August 31, 2013. The authors reported that 29 women of 13,221 (0.1%) undergoing medical abortion experienced a major complication, which was defined as including: emergency department presentation, hospitalization, infection, perforation and hemorrhage requiring transfusion. The article did not specify the rate of each event. No deaths or ectopic pregnancies were reported in this study. In 2011, Grossman<sup>36</sup> reported on a study of medical abortion provided through telemedicine, in which 578 women seeking abortion services at Planned Parenthood of the Heartland clinics in Iowa were offered in-person services or telemedicine services. The serious adverse event outcomes are reported in Table 12, Table 13 and Table 14 above, but in addition, he reported on adverse events among all medical abortion patients from July 1, 2008 through October 31, 2009 (a wider time frame than the study itself). Four of 1,172 telemedicine patients (0.3%) required a blood transfusion compared to 0.1% of 2,384 in-person patients. These figures were reported in the paper to support study findings of low rates of serious adverse events, including transfusion. Pena (2014)<sup>44</sup> reported on 1,000 women in Mexico who had a medical abortion up to 63 days gestation. Their paper reported that “there were no serious complications as defined by any occurrence that was unexpected, serious, and related to the induced abortion.” Upadhyay et al<sup>55</sup> used 2009 through 2010 patient-level billing data from Medi-Cal, California’s state Medicaid program, to evaluate the incidence of complications after abortion, including medical abortion. Major complications were defined as those which required hospitalization, surgery or blood transfusion. There were 11,319 medical abortions, with 35 women (0.31%) having a major complication.

Winikoff (2012)<sup>19</sup> provides data on other serious adverse events through 70 days. Regarding hospitalization, there were zero hospitalizations among 350 women receiving medical abortion at 64-70 days compared with 2/379 women at 57-63 days (0.5% rate). There were no serious infections in the 64-70 day group, compared with 1/379 (0.3% rate) in the 57-63 day group. There was one transfusion (1/350=0.3% rate) in the 64-70 day group, compared with 2/379 (0.5% rate) in the 57-63 day group.

**Reviewer comments:**

(b) (4)  
**. Serious adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are rarely reported in the literature. The rates, when noted are exceedingly rare, with rates generally far below 1.0% for any individual adverse event. This indicates that medical abortion with the proposed regimen up through 63 days is safe.**

<sup>55</sup> 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.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

**Serious fatal or nonfatal adverse events in the 64-70 days gestation group, were evaluated in one US study (Winikoff 2012)<sup>19</sup>. This study with 379 women in the 64-70 day range is reassuring in that the rates of hospitalization, serious infection and transfusion are no higher than in the lower gestational age ranges. Based on the available safety data on medical abortion in totality, it appears that serious fatal or nonfatal adverse events are very rare through 70 days as well. This regimen should be approved for use through 70 days gestation.**

**Reviewer's Final Recommendation:**

**The regimen of mifepristone 200 mg followed by misoprostol 800 mcg buccally in 24-48 hours is safe to approve for use through 70 days gestation.**

**7.3.3 Dropouts and/or Discontinuations**

The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc 2014<sup>16</sup>) to 22% in the Grossman<sup>36</sup> study using telemedicine to deliver medical abortion services. One study noted no differences in demographics between the subjects on whom follow-up was available, compared with those on whom no follow-up information was available. Only two studies evaluated other subgroups of women lost to follow-up. Gatter et al 2015<sup>13</sup> found a higher odds of loss to follow-up with age <18 and with income at or below the federal poverty level. Additionally they noted increased odds of loss to follow-up with increasing gestational age. As compared with women 43-49 days gestation, the Odds Ratio (OR) for loss to follow-up at 50-56 days was 1.17 (95% CI 1.05-1.31) and at 57-63 days was 1.28 (95% CI 1.10-1.48). The Boersma study<sup>22</sup> had a 7% loss to follow-up rate. The rate of loss to follow-up was 6.5% at ≤ 49 days, 7.6% at 50-63 days and 7.7% at 64-70 days. No tests for significance were applied to these numbers. Only one study reported on withdrawals: Winikoff 2012<sup>19</sup> reported that 0.27% of patients withdrew and noted this was similar to rates previously reported in the literature.

**Reviewer comment:**

**There is a wide range of loss to follow-up in the studies submitted with the efficacy supplement. The loss to follow-up rate cannot be reliably linked to method of follow-up, though it is notable that the lowest rate of loss-to-follow-up occurred in the Ngoc trial with telephone follow-up (0.6%) and the highest with abortion services provided via telemedicine (22%). The range of loss to follow-up is well-within the range documented in literature covering real-world abortion practice.<sup>1</sup>**

**7.4 Significant Adverse Events**

The label for misoprostol currently includes a boxed warning against the use past 8 weeks gestation, due to the risk of uterine rupture. The (b) (6) safety reviewer and

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

(b) (6) conducted separate literature searches on this topic. Chen et al 2008<sup>56</sup> evaluated 488 women with a mean gestational age of 7.8 weeks who received 800 mcg misoprostol as part of a randomized study of misoprostol vs. curettage for early pregnancy failure. They found that 78 (16%) of women in the misoprostol group had previous uterine surgery (>1 C-section or myomectomy). There were no uterine ruptures in that study. Gautam et al<sup>57</sup> reported in 2003 on 66 women up to 60 days' gestation and with previous Caesarean section scar, who received misoprostol 800 mcg for termination and found no uterine ruptures. The literature search also revealed five case reports of uterine rupture.<sup>58, 59, 60, 61, 62</sup> Of these five cases, three occurred with combined mifepristone/misoprostol dosing. Four women had uterine scars, most commonly from at least one prior cesarean section, and one of them had had a prior uterine rupture in labor. Only one woman had no prior uterine scar (Willmott). In these case reports and studies, women received varying doses of misoprostol ranging from 400 mcg to 600 mcg to 800 mcg, and in two, the women received multiple doses of misoprostol (4 and 5 doses in the Wilmot and Bika reports respectively). The women required surgery to repair the uterus or hysterectomy and transfusion. See Table 15.

APPEARS THIS WAY ON ORIGINAL

---

<sup>56</sup> Chen BA, Reeves MF, Creinin MD, Gilles JM, Barnhart K, Westhoff C, Zhang J. National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial. *Am J Obstet Gynecol* 2008;198(6):626. d1-5 doi: 10.1016/j.ajog.2007.11.045. Epub Feb 15, 2008.

<sup>57</sup> Gautam R, Agrawal V. Early medical termination pregnancy with methotrexate and misoprostol in lower segment cesarean section cases. *J Obstet Gynaecol Res* 2003; 29(4):251-256.

<sup>58</sup> Khan S, et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. *J Obstet Gynaecol* 2007;27(8):869-870.

<sup>59</sup> Kim JO, et al. Oral misoprostol and uterine rupture in the first trimester of pregnancy: A case report. *Reproductive Toxicology* 2005;20:575–577.

<sup>60</sup> Jwarah E, Greenhalf JO. Rupture of the uterus after 800 micrograms misoprostol given vaginally for termination of pregnancy. *BJOG* 2000;107:807.

<sup>61</sup> 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.

<sup>62</sup> Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. *BJOG* 2008;115:1575-1577.

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

**Table 15: Uterine Rupture with Misoprostol Case Reports**

Study	GA (weeks)	Mifepristone used?	Dose of Misoprostol	Number of doses of misoprostol	Risk Factor for Rupture
Khan <sup>58</sup>	8	Yes; dose not specified	600 mcg	1	1 prior C-section, 1 prior uterine rupture at 32 weeks
Kim <sup>59</sup>	8	No	400 mcg	1	1 prior C-section
Jwarah <sup>60</sup>	8 2/7	No	800 mcg	1	1 prior C-section
Bika <sup>61</sup>	10 2/7	Yes; 200 mg	800 mcg x 2 doses then 400 mcg x 2 doses	4	2 prior C-sections
Willmott <sup>62</sup>	12 3/7	Yes; 200 mg	400 mcg	5	none

Source: NDA clinical reviewer table.

(b) (6) also conducted a review of FAERS cases from January 1, 1965 through October 15, 2015 for reports of uterine rupture with mifepristone alone, misoprostol alone, or a combined regimen, with special interest in cases occurring in women  $\leq 10$  weeks pregnant ( $\leq 70$  days). The FAERS search retrieved 80 cases of uterine rupture, with 77 citing misoprostol use alone and 3 citing both mifepristone and misoprostol use. No cases of uterine rupture were reported with mifepristone use alone. Vaginal administration of misoprostol was documented in the majority of the cases. The majority of the FAERS cases either occurred in the 3rd trimester of pregnancy, or did not report gestational age. In the cases where the gestational age was not reported, it is likely that most of these cases occurred during the 2nd or 3rd trimester, as many noted the induction of labor as the reason for misoprostol use. The majority of cases also noted at least one additional potential risk factor, with a history of at least one previous c-section, or the use of additional uterotonic drugs (e.g., oxytocin or dinoprostone) being the most commonly reported. The use of misoprostol during the 3rd trimester for the induction of labor, cervical ripening, or both, in women that had at least one previous c-section, was also documented in many cases.

There were only two cases (2.5% of all reports) that reported uterine rupture within the first 10 weeks of pregnancy. In both cases, misoprostol alone was utilized for termination of pregnancy. The first case provided minimal information other than documentation of a 5 week gestation, and an ultrasound noting “an important uterine separation” during an unspecified time after misoprostol (route not specified) administration. The remaining case was also a published case report in which uterine rupture was documented as occurring approximately 2.5 hours after 800 mcg of misoprostol was administered vaginally for cervical preparation prior to surgical termination of pregnancy. The patient was 8 weeks and 2 days pregnant, had a history of a prior c-section, and was of advanced maternal age. (b) (6) concluded that uterine



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

rupture associated with the use of mifepristone alone, misoprostol alone, or both, is likely a rare event in the 1st trimester.

**Reviewer comment:**

**Based on the scarcity of reported cases in the first trimester of pregnancy, uterine rupture associated with early medical abortion using mifepristone with or without misoprostol is likely rare. There are a three reports of uterine rupture with mifepristone and misoprostol in the first trimester, most of which occurred in women with prior uterine surgery (e.g., a cesarean section).**

**7.4.1 Submission-Specific Primary Safety Concerns**

**Summary of requested dosing changes in the NDA Supplement that could affect safety:**

**1. Proposing a new dosing regimen that uses mifepristone 200 mg oral and the buccal administration of 800 mcg misoprostol at 24-48 hours after Mifeprex and increasing the gestational age from 49 days to 70 days**

The Applicant submitted several articles in support of the proposed dosing regimen as well as increasing the gestational age through 70 days using the proposed regimen, including the 24-48 hour interval. See Section 7.3 Major Safety Results for fatal and nonfatal serious adverse events reported with the proposed regimen and gestational age. The data submitted show these events to be exceedingly rare, indicating that the new dosing regimen and increasing the gestational age to 70 days is safe. Please see Section 7.3 Major Safety Results on Nonfatal Serious Adverse Events for a review of this information.

In further support of changing the dosing interval for misoprostol to 24-48 hours after mifepristone is taken, the Applicant also provided a systematic review by Shaw et al.<sup>63</sup> In this study the authors searched Medline, ClinicalTrials.gov, Popline and the Cochrane Controlled Trials Register and included 20 randomized controlled trials and 9 observational studies. The majority of the studies used the proposed 200 mg dose of mifepristone, but three RCTs and two observational studies used 600 mg of mifepristone. The doses and route of misoprostol administration varied, including doses of 400 mcg, 600 mcg, and 800 mcg, some with repeat doses, and included vaginal, buccal, oral and sublingual routes. There was wide variation in time to administration of the misoprostol, ranging from <24 hours, 24-48 hours, 36-48 hours. Adverse events were not reported consistently. There was no statistically significant difference in nausea, vomiting or diarrhea.

---

<sup>63</sup> 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.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

**Reviewer comment:**

**Unlike the efficacy data, which is based on studies that look specifically at individual changes proposed by the Applicant, the adverse event data typically come from studies or reviews that include multiple changes (e.g., dose of each drug, dosing interval, gestational age) simultaneously. Therefore, it is not possible to provide safety data specific to each individual change.**

**The changing of the dosing interval to 24-48 hours does not appear to increase the risk of serious fatal or nonfatal adverse events or to increase the risk of common adverse events associated with medical abortion.**

**Reviewer's Final Recommendation:**

**Based on the available evidence, changing the dosing interval between mifepristone and misoprostol to 24-48 hours is safe to approve, including for use in gestations up through 70 days.**

**2. Home administration of misoprostol**

Currently, the Dosage and Administration section of labeling for Mifeprex requires that patients return to the healthcare provider on Day 3 (two days after ingesting Mifeprex) for misoprostol. The Applicant proposes that the label be changed to allow for home administration of the misoprostol. The Applicant reasons that all published US trials after the initial trial by Spitz et al<sup>26</sup>, as well as numerous international trials, included distribution of misoprostol for self-administration at home with evidence of safe and effective medical abortion. The Applicant also emphasizes that women usually start having bleeding within two hours of administration of the misoprostol and home administration gives the opportunity for more privacy in the process.

The Applicant submitted many articles to support this change. See Table 8 for US and foreign studies that enrolled over 30,000 women who administered misoprostol at home. None of the studies directly compare home versus clinic/office administration of misoprostol. Most of the studies include protocols where all of the subjects take misoprostol at home. Gatter<sup>13</sup> and Ireland<sup>15</sup> reported separately on large numbers of clients of Planned Parenthood Los Angeles (13,373 and 13,221 clients respectively, though likely with some overlap, in 2010-2011), while Winikoff (2012<sup>19</sup> and 2008<sup>23</sup>), Grossman<sup>36</sup>, Creinin<sup>25</sup> and Middleton<sup>24</sup> reported on smaller numbers of US subjects. Internationally, Goldstone<sup>20</sup> reported on 13,345 medical abortions, while Kopp Kallner<sup>64</sup>, Løkeland<sup>65</sup>, Chong (2012)<sup>40</sup>, Bracken<sup>49</sup>, Pena<sup>44</sup>,

---

<sup>64</sup> 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.

<sup>65</sup> Løkeland M, Iversen OE, Engeland A, Økland I. Medical abortion with mifepristone and home administration of misoprostol up to 63 days' gestation. *Acta Obstet Gynecol Scand* 2014;93:647-653.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

Ngoc<sup>16</sup>, Louie<sup>14</sup>, Sanhueza Smith<sup>48</sup>, Boersma<sup>22</sup> and Lynd<sup>66</sup> report on smaller numbers of subjects. All of these studies have been reviewed above in Sections Deaths, Nonfatal Serious Adverse Events and Common Adverse Events. This information shows that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the original studies of clinic administration of misoprostol.

Swica et al<sup>50</sup> similarly conducted a non-randomized trial with 301 US women, 139 of whom chose home use of mifepristone and misoprostol and 162 of whom chose clinic administration of mifepristone followed by home use of misoprostol. The majority of women (74%) who chose home use took the mifepristone at the appointed 6-48 hour window; for those who took it at a different time than that planned with their provider, the median interval was 25 hours. Over 90% of women in both groups took the misoprostol at the scheduled time, and none waited past 72 hours to take the misoprostol. There were no significant differences in the mean number of days of work or school missed or dependent care needed. Most women made no additional calls (85% for home use group and 90% for office use group) or unscheduled visits to the doctor's office (96% for home use group and 99% for office use group).

The Applicant also submitted a commentary by Gold and Chong<sup>67</sup>, in which they discuss benefits of home administration of Mifeprex and misoprostol. They cite the convenience of scheduling for women, the possibility of greater autonomy and privacy, the lack of burden on staff, and the safety.

**Reviewer comment:**

**Home use of misoprostol has been evaluated as part of the proposed protocol in studies including well over 30,000 patients, as well as in dedicated studies of home use of mifepristone and misoprostol. The studies demonstrate that women take the misoprostol at the recommended time. The safety profile is acceptable, with rates of adverse events equal to or lower than those with the approved regimen requiring in-office dispensing of misoprostol. The studies, including those of home use of mifepristone and misoprostol, show increased convenience, autonomy and privacy for the woman, a smaller impact on their lifestyles, and no increased burden on the healthcare system. The safety data on the home use of misoprostol are adequate to support revision of labeling.**

---

<sup>66</sup> Lynd K, Blum J, Ngoc NTN, Shochet T, Blumenthal PD, Winikoff B. Simplified medical abortion using a semi-quantitative pregnancy test for home-based follow-up. *Int J Gynecol Obstet* 2013;121:144-148.

<sup>67</sup> Gold M, Chong E. If we can do it for misoprostol, why not for mifepristone? The case for taking mifepristone out of the office in medical abortion. *Contraception* 2015;92:194-196.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

**Reviewer's Final Recommendation:**

**Based on the available data, home use of misoprostol is safe to approve.**

**3. Repeat dose of misoprostol if needed.**

The Applicant reasoned that studies include an option for a repeat dose of misoprostol to allow women to avoid a surgical procedure if possible and that this is a safe way to treat an incomplete medical abortion. The Applicant submitted two articles on the repeat use of misoprostol, one randomized trial and one systematic review, that were relevant to this safety review (other articles<sup>12, 17, 22</sup> did not present safety data stratified by number of misoprostol doses). Only one randomized trial reviewed the safety of repeat misoprostol. Coyaji et al<sup>68</sup> conducted a randomized controlled trial of 300 women seeking medical abortion in India. After taking mifepristone, women in one group took 400 mcg misoprostol followed by placebo 3 hours later, while women in the other group took two doses of 400 mcg misoprostol 3 hours apart. As discussed in the efficacy portion of this review, there was no significant difference in the complete abortion rate between the groups; however, the repeat misoprostol reduced need for surgical intervention. Before discharge home, there was no significant difference in the adverse effects observed—similar percentages of women experienced cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). More women in the repeat dose arm experienced moderate to severe cramping than women in the single dose arm on Day 4 (24% versus 15%,  $p=0.032$ ) and on Day 7 (10% versus 4%,  $p=0.006$ ).

Gallo<sup>69</sup> performed a systematic review of data relating to the safety and efficacy of more than one dose of misoprostol after mifepristone for medical abortion. The search yielded three randomized controlled trials that studied medical abortion  $\leq 63$  days. The studies included doses of mifepristone ranging from 200 mg to 600 mg followed by misoprostol 6 to 48 hours later, in doses ranging from 400 mcg to 800 mcg via the oral, sublingual or vaginal routes. In two trials, all subjects received repeat misoprostol—in one, three hours later, while in the other study subjects received misoprostol twice a day for days 4-10. In the third trial, subjects only received repeat misoprostol if there was still a gestational sac present. The only side effects discussed in the trials were diarrhea, which was more common in those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported  $<1\%$ .

There is a good deal of literature on the use of misoprostol alone for medical abortion and in those regimens, doses of up to 800 mcg repeated in three hours have been

---

<sup>68</sup> 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.

<sup>69</sup> 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.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

used. In a study by Blum et al<sup>70</sup>, misoprostol only, given as two doses of 800 mcg three hours apart, was compared to mifepristone-misoprostol medical abortion where only one dose of 800 mcg misoprostol was administered. The two groups had similar rates of nausea, vomiting, fever and chills. Subjects in the repeat misoprostol group had more diarrhea than in the mifepristone-misoprostol group (83.9% vs. 61.2%, p<0.001). Please see Section 7.4 Significant Adverse Events for additional discussion on safety concerns with repeat doses of misoprostol.

**Reviewer comment:**

**There are few articles concerning the safety of repeat misoprostol after mifepristone administration. Generally, the success of mifepristone-misoprostol medical abortion renders the need for a second dose of misoprostol to be relatively uncommon. In studies of misoprostol alone given using a single repeat dose, there is an increased risk of the common adverse event of diarrhea. There have been rare reports of uterine rupture in women with a prior uterine scar who receive repeated doses of misoprostol.**

**Reviewer's Final Recommendation:**

**Based on the available data, the option for repeat misoprostol in women whose pregnancy has been terminated, but who have not completely expelled the pregnancy is safe and should be approved. For women whose pregnancy is ongoing at follow-up, surgical intervention is recommended, rather than repeated misoprostol. The rare reports of uterine rupture in women with a prior uterine scar who receive repeated doses of misoprostol is discussed in labeling.**

**4. Follow-up timing and method: follow-up is needed, but not necessarily in the clinic or licensed healthcare provider's office at 14 days after mifepristone administration**

The Dosage and Administration section of the current approved label for Mifeprex stipulates that patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred. The Applicant acknowledges that follow-up is important to diagnose and treat complications, and to ensure complete abortion or identify ongoing pregnancies. However, the Applicant proposes to change the labeling to state that the provider should perform an assessment at 1-2 weeks, in order to broaden the timeframe and method used, to give patients and providers more flexibility and reduce loss to follow-up rates. Use of ultrasound, serum and urine pregnancy testing (semi-quantitative, and quantitative) and telephone calls have all been evaluated in the literature as options for follow-up of patients after medical

---

<sup>70</sup> Blum J, Raghavan S, Dabash R, Ngoc NTN, Chelli H, Hajri S, Conkling K, Winikoff B. comparison of misoprostol-only and combined mifepristone-misoprostol regimens for home-based early medical abortion in Tunisia and Vietnam. Int J Gynecol Obstet 2012;118:166-171.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

abortion. Grossman and Grindlay<sup>71</sup> conducted a systematic review of the literature on alternatives to ultrasound for medical abortion follow-up. They identified eight studies, but found that outcomes of interest (ongoing pregnancy) were rare with medical abortion and not consistently defined across studies. Nonetheless, they found that serum hCG, a low sensitivity urine pregnancy test combined with a standardized assessment with multiple questions about women's symptoms, or standardized telephone follow-up, perhaps followed by high-sensitivity urine pregnancy test, all had sensitivities  $\geq 90\%$  and negative predictive values (NPVs)  $\geq 99\%$  and they resulted in a proportion of "screen positives (or women who had a self-assessment of ongoing pregnancy and had an unscheduled visit)  $\leq 33\%$ ."

This reviewer analyzed relevant studies that were submitted by the Applicant and referenced in the Grossman and Grindlay assessment.<sup>71</sup> Perriera et al<sup>21</sup> conducted a prospective cohort study of 139 US women with  $\leq 63$  days gestation undergoing medical abortion at one center. Up to three attempts were made to phone subjects 7 days after taking mifepristone. The subjects were asked to confirm when they took misoprostol and generally to describe their experience. They were then asked a series of five standardized questions to assess for expulsion, including:

- 1 Did you have cramping and bleeding heavier than a period?
- 2 Did you pass clots or tissue?
- 3 What was the highest number of pads you soaked per hour?
- 4 Do you still feel pregnant now?
- 5 Do you think you passed the pregnancy?

If the clinician or the subject did not think the pregnancy had passed, the subject was asked to return to the center for an ultrasound within 7 days. If there was an ongoing pregnancy, women were offered additional misoprostol or a D&C. If the clinician and subject believed the pregnancy had passed, she was instructed to begin birth control or schedule a visit for injectable, implantable or intrauterine contraception. On Day 30, the subject was to perform a urine pregnancy test. Follow-up was obtained for 97.1% of subjects. Four subjects did not complete follow-up (2.9%)—one was never reached by phone, three were and two of them had positive pregnancy tests while one had an inconclusive test. These three never returned for an in-person visit and outcomes are not available on them. The sensitivity for correctly predicting an expelled pregnancy (completed abortion) was 95.9%, specificity was 50%, positive predictive value 97.5% and negative predictive value 37.5%. This study suggests that clinicians and subjects are almost always correct when they believe a pregnancy has passed. The loss to follow-up rate was not higher than for standard medical abortion follow-up.

Fiala et al<sup>72</sup> compared hCG with ultrasound for verification of completed abortion in 217 women  $\leq 49$  days with intrauterine pregnancy in Scotland. Successful expulsions were

<sup>71</sup> Grossman D, Grindlay K. Alternatives to ultrasound for follow-up after medication abortion: a systematic review. *Contraception* 2011;83:504-510.

<sup>72</sup> Fiala C, Safar P, Bygdeman M, Gemzell-Danielsson K. Verifying the effectiveness of medical abortion;



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

consistent with a marked decline in hCG values at follow-up. Using 20% of the initial value as cut-off at follow-up gave a high sensitivity. It allowed correct diagnosis in 98.5% of the patients with successful expulsion. When 20% of the initial hCG value was used as cut-off, a positive predictive value for successful expulsion was 99.5%. If the reduction of the hCG level was less than 80%, the negative predictive value was 50% and further evaluation was warranted. By contrast, the reliability of ultrasound examination in diagnosing successful expulsion was 89.8%.

Lynd et al<sup>66</sup> studied 300 women at  $\leq 63$  days gestation who underwent medical abortion in Vietnam. Women were given mifepristone and sent home with misoprostol and a semi-quantitative urine pregnancy test, a urine cup, instructions and a questionnaire. They were to take the urine test, record their impression of the results and complete the questionnaire on the morning of an in-person follow-up visit 2 weeks after mifepristone administration. Fifty-four women (18.5%) still felt pregnant at the follow-up visit, but only 11 of the semiquantitative urine tests indicated ongoing pregnancies. All 11 correctly identified ongoing pregnancies, with 100% sensitivity and 89.7% specificity. Ten of the 11 women with an ongoing pregnancy understood in-person follow-up was necessary.

Similarly, Cameron et al<sup>73</sup> reported on 1791 women undergoing medical abortion in Scotland, 1,726 (96%) of whom chose self-assessment with a low-sensitivity urine pregnancy test, instructions on how to interpret it, and signs/symptoms of ongoing pregnancy. The rest of the women chose in-clinic follow-up with an ultrasound or a phone call. Eight women in the self-assessment group had ongoing pregnancies, but only four of them had a positive low-sensitivity pregnancy test at the appointed time—within 4 weeks. Of the four who did not follow up in 4 weeks, two had a positive or invalid pregnancy test within two weeks after the medical abortion and should have presented for care, and two reported their pregnancy test was negative and did not present for care. All has successful termination either with repeat medical dosing or surgical aspiration. Most women presented within four weeks, but two women presented only after two missed menses. The delayed follow-up was not different from that for an in-person visit or an ultrasound.

**Reviewer comments:**

**While the number of articles is not extensive, they include almost 2,400 subjects. The Applicant demonstrates that alternatives to in-clinic follow-up are effective and safe, detecting most of the ongoing pregnancies so that women can get needed treatment. It appears that, using standardized questionnaires or instructions or a telephone call along with a low or high sensitivity pregnancy test, ongoing pregnancies can be detected allowing for further treatment. There is some loss-to-follow-up, but the rates do not appear to exceed those associated**

---

ultrasound versus hCG testing. Eur J Obstet Gynecol Reprod Biol 2003;109:190-195.

<sup>73</sup> 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.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

with a planned in-clinic follow-up. Women should be allowed to have an in-person visit if desired, but also allowed the flexibility of other options if desired.

It is important to note that since 2005, Planned Parenthood Federation of America has waived the follow-up visit if it poses undue hardships owing to distances from abortion facilities or other reasons, and women manage their follow-up with serial hCG testing.<sup>74</sup> From the clinical reviewers' perspective, this is safe and acceptable. We further note that the NAF 2015 guidelines (page 23) state the following:

“Success of the medical abortion must be assessed by ultrasonography, hCG testing, or by clinical means in the office or by telephone. If the patient has failed to follow-up as planned, clinic staff must document attempts to reach the patient. All attempts to contact the patient (phone calls and letters) must be documented in the patient's medical record.”

The ACOG 2014 Practice Bulletin<sup>1</sup> on management of early MAB states “Follow-up after receiving mifepristone and misoprostol for medical abortion is important, although an in-clinic evaluation is not always necessary.” Several options for follow up without an office/clinic visit are discussed and no specific method or algorithm is definitely recommended (i.e., it is left to the discretion of the provider and patient).

#### **Reviewer's Final Recommendation:**

Based on the available evidence, flexibility in the timing and method of follow-up is safe to approve.

## **7.5 Supportive Safety Results**

### **7.5.1 Common Adverse Events**

According to the currently approved Mifeprex label,<sup>75</sup> common adverse events include the following:

- Vaginal bleeding up to 16 days, with 8% of women experiencing bleeding up to 30 days. 4.8% of women in the original US trials and 4.3% in the original French trials required administration of uterotonic agents to control the bleeding. Only 1% of women required intravenous fluids and 1% required curettage. In the original French trials, 5.5% of women had a drop in hemoglobin of more than 2 g/dL.
- Abdominal pain in 96% of US women
- Uterine cramping in 83% of French women
- Nausea in 43-61%, vomiting in 18-26%

<sup>74</sup> Fjerstad M. Figuring out follow-up. Mife Matters. Planned Parenthood Federation of America/Coalition of Abortion Providers 2006;13:2-3.

<sup>75</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2000/20687lbl.htm](http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.htm)

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

- Diarrhea in 12-20%
- Headache in 2-31%
- Dizziness in 1-12%

A review of the literature submitted in the efficacy supplement, which includes Mifeprex at the proposed dose but also includes misoprostol administered buccally, vaginally or orally, reveals the following. Table 16 addresses bleeding that did not require transfusion (which is covered in Table 14: Transfusion by Gestational Age above), but was still significant in terms of requiring another intervention or in terms of a decrease in measured hemoglobin. Most of the studies include subjects up to 63 days' gestation, with the exception of Middleton 2005<sup>24</sup>, which includes subject to 56 days, and Sanhueza Smith 2015<sup>48</sup> and Winikoff 2012<sup>19</sup>, which include subjects through 70 days.

**Table 16: Bleeding and Cramping in Literature**

Study	N	Maximal Gestational Age	Route of misoprostol administration	Adverse Event Rate (%)		
				Bleeding requiring intervention*	Bleeding with drop in hemoglobin > 2g/dL	Cramping/pain
Middleton 2005 <sup>24</sup>	216	56 d	buccal	4.2	NR	NR
Coyaji 2007 <sup>68</sup>					NR	87-89
Løkeland 2014 <sup>65</sup>				4.9	NR	96.6
Kopp Kallner 2010 <sup>64</sup>	395	63 d	vaginal	0.5	NR	NR
Pena 2014 <sup>44</sup>	971	63 d	Buccal	1.7	NR*	NR
Ngoc 2014 <sup>16</sup>	1433	63 d	buccal	0.07	NR	NR
Gatter 2015 <sup>13</sup>	13,373	63 d	buccal	1.8	NR	NR
Ireland 2015 <sup>15</sup>	13,221	63 d.	buccal	1.8	NR	NR
Winikoff 2012 <sup>19</sup>	729	70 d	buccal	1.1	NR	NR
Sanhueza Smith 2015 <sup>48</sup>	960	70 d	buccal	1.7	NR	NR

\*Intervention includes aspiration or uterine evacuation, use of uterotonics, intravenous fluids

\*NR=not reported

Source: NDA clinical reviewer table.

**Reviewer Comments:**

Given that Mifeprex and misoprostol are taken to terminate an intrauterine pregnancy, vaginal bleeding and cramping or abdominal pain are an expected



Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

**and necessary part of the process; therefore, these should only be considered adverse events if the amount of bleeding or pain exceeds what would be expected for such a process. The rate of bleeding requiring intervention is low and ranges from 0.5% to 4.2%, with the rates in the largest studies being around 1.8%. Two articles parsed the bleeding requiring intervention by gestational age. In Sanhueza Smith et al.<sup>48</sup> the rate was 1.1% (7/622) among women  $\leq$  56 days, 4.2% (8/190) in women 57-63 days and 1.4% (2/148) in women 64-70 days. In Gatter 2015<sup>13</sup>, the rate was 0.65-1.43% up to 49 days, 2.04% in women 50-56 days, and 2.49% in women 57-63 days. These differing numbers from the two studies do not reveal a trend toward bleeding requiring intervention with increasing gestational age, specifically even through 70 days.**

**No articles submitted discussed a drop in hemoglobin of  $> 2$  g/dL, most likely because routine laboratory studies are not obtained in medical abortion unless anemia or a medical illness is reported or suspected. Also not surprisingly, pain and cramping are an expected part of the medical abortion process, so most studies do not comment on the percentage of women who experience this.**

APPEARS THIS WAY ON ORIGINAL

Clinical Review

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

NDA 020687/S-020- Mifeprex

**Table 17: Common Adverse Events in Literature**

Study	N	Maximal GA (days)	Route of Misoprostol	Adverse Event Rate (%)							
				nausea	vomiting	diarrhea	fever	chills	headache	dizziness	weakness
Middleton 2005 <sup>24</sup>	216	56 d	Buccal	70	37	36	42	NR	44	41	51
Blum 2012 <sup>70</sup>			buccal	45.9	37.8	61.2	28.2	30.6			NR
Coyaji 2007 <sup>68</sup>				1	0-2	NR*	NR	NR			NR
Kopp Kallner 2010 <sup>64</sup>	395	63 d	vaginal	87.1	57.3	6.3	26.3	NR	4.1	3.6	2-3.1
Louie 2014 <sup>14</sup>	860	63 d	buccal	38-53	13-25	1-3	15-23†				NR
Pena 2014 <sup>44</sup>	971	63 d	buccal	NR	NR	7.8	8.9†	†	NR	NR	14.3
Creinin 2007 <sup>25</sup>	544	63 d	vaginal	9.4	5.7	4.8	10.3†	†	6.6	6.8	NR
Chong 2012 <sup>40</sup>	563	63 d	buccal	47	22	NR	33†	†	33	24	42
Winikoff 2012 <sup>19</sup>	618	70 d	buccal	50.8	40.6	17.6	11.2	23.5	NR	NR	NR
Sanhueza Smith 2015 <sup>48</sup>	960	70 d	buccal	27	23	44.6	46†	†	14.3	9.7	21

GA = gestational age; \*NR= not reported. † includes fever and chills, which were grouped together

Source: NDA clinical reviewer table.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

**Reviewer comment:**

The range of reported percentages for each adverse event is wide, with some studies reporting virtually no patients experiencing nausea, vomiting or diarrhea, while others report at least half of subjects suffering these side effects. Only the Winikoff 2012<sup>19</sup> article parses out these side effects by gestational age (57-63 days versus 64-70 days). There is no statistically significant difference in the rates of any side effect between gestational age group except for vomiting, where 35.8% of women 57-63 days had vomiting and 45.7% of women 64-70 days did (p=0.008). It is hard to determine a value that could be used in labeling based on these wide variations, but the adverse events are common, expected and well-known with the medical abortion regimen and the ranges should be reported in labeling.

**7.5.2 Laboratory Findings**

Mifepristone with misoprostol is a well-established regimen for termination of pregnancy. Few laboratory tests are necessary before use of the regimen. Those that are commonly performed include confirmation of pregnancy (urine or serum pregnancy testing) as well as Rh testing (unless it has been previously documented), such that RhD immunoglobulin can be administered as indicated. Pre-medical abortion assessment of hemoglobin or hematocrit is indicated when anemia is suspected. Routine follow-up laboratory testing is also not indicated unless dictated by the patient's clinical condition, for example, heavy bleeding or signs of infection. Lab results are not typically reported in the literature, except for when studies look at decreases in hemoglobin related to bleeding.

**7.5.3 Vital Signs**

Vital signs are not typically reported in the literature on medical abortion.

**7.5.4 Electrocardiograms (ECGs)**

Mifepristone used with a prostaglandin analogue has been approved for medical termination of pregnancy since 1988 in France and subsequently in many countries around the globe. It has been well-established that doing an ECG prior to MAB is not standard procedure. It can be done if individual circumstances warrant its use. Literature does not typically report on ECGs.

**7.5.5 Special Safety Studies/Clinical Trials**

The pediatric studies are addressed in Section 7.6.3.

**7.5.6 Immunogenicity**

NA to this review

**7.6 Other Safety Explorations**

This section is not relevant to this application.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

### 7.6.1 Additional Safety Evaluations

### 7.6.2 Human Carcinogenicity

The Applicant submitted no new data on human carcinogenicity.

### 7.6.3 Human Reproduction and Pregnancy Data

As noted in the efficacy portion of this review, some women who use Mifeprex do have ongoing pregnancies. Most of these are treated with an aspiration or a surgical evacuation of the uterus; there is little information on outcomes of ongoing pregnancies not terminated by another method. At the time of approval of the drug, the Applicant agreed to two postmarketing commitments, including one to conduct a surveillance study of the outcomes of ongoing pregnancies. On January 11, 2008, the Applicant was released from this commitment due to the lack of an adequate number of women enrolled. The Applicant explained that the small number was due, in part, to the requirement that the patients consent to participation [*in the surveillance study*] after seeking a pregnancy termination.

A review of all of the articles submitted by the Applicant for outcomes of ongoing pregnancies after mifepristone administration yielded minimal information. There is one article reporting a case of a fetus with sirenomelia, a cleft palate and lip, micrognathia, and hygroma; this infant was born to a woman who had received mifepristone as RU 486 at 18 weeks and was reported to Roussel-Uclaf in France in 1989.<sup>76</sup> A prospective observational study<sup>77</sup> from fifteen French pharmacovigilance centers followed women exposed to mifepristone in the first trimester between 1997 and 2010. The study included pregnant women who sought counseling on mifepristone exposure from a pharmacovigilance center or Paris Teratology Information Service (TIS). A total of 105 pregnancies were exposed to mifepristone in the first trimester; 46 to mifepristone alone, and 59 to mifepristone and misoprostol. The mean gestational age at exposure was 7.9 weeks; 81% were exposed between weeks 5 and 9 of gestation. About 40% of patients received 200 mg of mifepristone while about 50% received 600 mg. Of the patients who received both mifepristone and misoprostol, 48 received repeat misoprostol with four receiving 1200–2000 mcg of misoprostol, a significantly higher dose than recommended. Among all exposed women, there were 94 live births (90.4%), 10 (9.6%) miscarriages (including one with a major malformation of major hydrocephalus associated with adductus thumb and a normal karyotype) and one patient had an elective termination of pregnancy for the subsequent diagnosis of trisomy 21. Eight of the ten miscarriages occurred in the mifepristone-only group; however, after potential confounding factors such as maternal age, gestational age at inclusion,

<sup>76</sup> Pons JC, Papiernik E. Mifepristone teratogenicity. *Lancet* 1991;338(8778):1332-3.

<sup>77</sup> Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, Amar E, Descotes J, Vial T. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. *BJOG* 2013;120:568–575.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

drug exposure, and mifepristone dose were controlled for by logistic regression, the rate of miscarriage did not differ across mifepristone only versus mifepristone-misoprostol groups ( $p= 0.08$ ). Among the live births, the mean gestational age at delivery was 39.5 weeks and there was no difference in birth weights between groups. The overall rate of major congenital malformations among the 95 examinable cases was 4.2% (95% CI 1.2–10.4%), with two cases among 38 patients exposed to mifepristone alone, and two cases among 57 patients exposed to both mifepristone and misoprostol. Three of the four major congenital malformations occurred with exposure to 600 mg of mifepristone, while one occurred in exposure to 400 mg of mifepristone. The malformations included:

- Claude Bernard–Horner syndrome with stridor
- Hydrocephalus with triventricular dilatation and adductus thumb (miscarriage patient noted above)
- Möbius syndrome
- Retrognathism, slight cleft palate, trismus, swallowing disorder, club foot with four toes, incomplete genital development and mild hypoplasia of the cerebellar vermis

The authors posit that the cases of major malformations in patients exposed to mifepristone alone could be explained by associated medical conditions, for example, the case of congenital Claude Bernard Horner syndrome could have been related to traumatic vaginal delivery of a high birth weight newborn, a well-recognized cause of this syndrome, while the spontaneously aborted hydrocephalic fetus may have been caused by streptococcus B chorioamnionitis, which was subsequently confirmed on pathological examination, or be an X-linked hydrocephalus. The authors also note that the two cases of major malformations in patients exposed to both mifepristone and misoprostol were consistent with malformations described after exposure to misoprostol alone. The authors concluded that major malformations after first-trimester exposure to mifepristone is only slightly higher than the expected 2–3% rate in the general population, which was reassuring regarding the risk evaluation for continuation of pregnancy after mifepristone exposure.

There are reports that misoprostol can result in congenital anomalies when used during the first trimester, including defects in the frontal or temporal bones, limb abnormalities with or without Mobius syndrome.<sup>1</sup> The Korlym label notes in Important Safety Issues with Consideration to Related Drugs: “In a report of thirteen live births after single dose mifepristone exposure, no fetal abnormalities were noted.”

**Reviewer Comment:**

**There are anomalies associated with the use of misoprostol in the first trimester. The risk of teratogenic effects with a continued pregnancy after a failed pregnancy termination with Mifeprex in a regimen with misoprostol is unknown. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with Mifeprex in a regimen with misoprostol, but it is not clear if this just represents the usual background rate of birth defects.**

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

**As discussed above, FDA requested at the time of initial approval that the Applicant conduct a surveillance study of the outcomes of ongoing pregnancies. The Applicant was subsequently released from this commitment because it had been unable to enroll a sufficient number of women with ongoing pregnancies after an attempted medical abortion in the surveillance study.**

#### 7.6.4 Pediatrics and Assessment of Effects on Growth

The Applicant submitted no new data on assessment of effects on growth in pediatric patients. The Applicant did submit data on efficacy and safety of medical abortion in adolescents, using the proposed regimen of 200 mg oral Mifeprex followed by 800 mcg buccal misoprostol 24-48 hours later at home, in order to satisfy requirements for PREA. Gatter et al (2015)<sup>13</sup> included data on 322 adolescents. (b) (6), (b) (4)

The adolescent efficacy was similar to that of all older women; this implies that compliance in taking the misoprostol dose properly at home was also acceptable. The study included adolescents aged 11-16 per Table 18 below:

**Table 18: Age of Adolescents Undergoing Medical Abortion**

Age	# Subjects
11	1
12	1
13	2
14	20
15	82
16	216

Source: (b) (6), (b) (4) NDA 20687s20

(b) (4), (b) (6) As is evident in the table, no adolescents had a hospitalization, severe infection or hemorrhage which required a transfusion.

**Table 19: Serious Adverse Events in Adolescents vs. Adults**

	Under 17	17+	All
<b>Transfusion</b>	0.00% (0/251)	0.03% (4/13,122)	0.03% (4/13,373)
<b>Hospitalization</b>	0.00% (0/251)	0.05% (7/13,122)	0.05% (7/13,373)
<b>Infection</b>	0.00% (0/251)	0.02% (2/13,122)	0.01% (2/13,373)

Source: (b) (6), (b) (4) NDA 20687s20

In 2011, Niinimäki et al<sup>54</sup> published a retrospective cohort study of the Finnish abortion registry from 2000-2006, in which they evaluated the rates of adverse events in 3,024



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

adolescents and 24,006 adult women undergoing medical abortion (regimen unspecified). The study population included women  $\leq 20$  week's gestation; 84.6% of the adolescents were  $\leq 12$  weeks, while 86.6% of the adults were  $\leq 12$  weeks. Adolescents ranged in age from 13-17, with a mean age of 16.1 years. The study showed that after adjustment for parity, previous abortion, marital status, types of residence, duration of gestation and year of abortion, in adolescents, the adjusted ORs were significantly lower for hemorrhage (0.87, 95% CI 0.77 to 0.99), incomplete abortion (0.69, 95% CI 0.59 to 0.82) and surgical evacuation (0.78, 95% CI 0.67 to 0.90) compared to adults. There was no significant difference in the OR for infection (0.97, 95% CI 0.73 to 1.30).

Phelps<sup>53</sup> had previously conducted a pilot study in 28 adolescents aged 14-17, at  $\leq 56$  days gestation, using Mifeprax 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. As reported in Section Subpopulations, 100% of study subjects had a complete abortion, with five not requiring misoprostol. There were no serious adverse events. Subjects noted common expected adverse events including bleeding (100%), cramping (95%), nausea (62%), and vomiting (43%).

It is also important to consider adherence to the proposed regimen (including taking misoprostol at a location other than the clinic) and adherence to follow-up among adolescents versus adults.

There are no data specifically comparing adherence to the regimen among adolescents  $<17$  with women  $\geq 17$  years old. The Gatter<sup>13</sup> study clearly demonstrates the efficacy and safety is the same for both age groups, suggesting that there is no clinically significant difference in adherence to the regimen between age groups. The Goldstone<sup>20</sup> article included 8 subjects aged 14 and 931 subjects aged 15-19. The efficacy and safety are not separated out by age; however, all subjects did take the proposed regimen and overall efficacy and safety is reassuring, indicating that adolescents and adults alike likely did adhere to the mifepristone and misoprostol regimen in a safe and effective way.

Regarding adherence to follow-up, four articles included 346 subjects  $<17$  years old. Ngoc<sup>16</sup> is based in Vietnam and Cameron<sup>73</sup> is based in Scotland, while Gatter<sup>13</sup> and Horning<sup>78</sup>, are US-based studies. (b) (4), (b) (6)

. The difference in the follow-up rate for the combined data is 6.5%. The Gatter study accounts for 85% of all patients being compared. The difference in follow-up adherence is not clinically relevant as there is no difference in efficacy between the two age groups.

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

**Table 20: Adherence to Follow-Up Among Adolescents vs. Adults**

	<17 years old			≥17 years old		
	N	# Adherent	Adherence %	N	# Adherent	Adherence %
Gatter <sup>13</sup>	322	251	78.0%	15,517	13,122	84.6%
Cameron <sup>71</sup>	5	4	80.0%	607	516	85.0%
Ngoc <sup>16</sup>	1	1	100.0%	1,406	1,345	95.7%
Horning <sup>78</sup>	18	16	88.9%	846	648	76.6%
TOTAL	346	272	78.6%	18,376	15,631	85.1%

**Reviewer Comment:**

Medical abortion in adolescents appears to be at least as safe, if not safer, as in adult women. Adolescents appear able to comply with the regimen, including use of misoprostol outside of the clinic setting, as well as with alternative follow-up methods. These data support the safety of Mifeprex in adolescents and satisfy requirements for PREA. No information on safety and efficacy of use in premenarchal girls is required, as the medication is not indicated in that subset of the pediatric population.

**Reviewer's Final Recommendation:**

The available evidence supports that Mifeprex and the new proposed dosing regimen are safe to use in adolescents.

**7.6.5 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

The Applicant submitted no new data on overdose, drug abuse potential withdrawal and rebound.

**7.7 Additional Submissions / Issues**

Summary of additional changes in labeling that may affect safety of Mifeprex

**1. Change in labeled time for expulsion from 4-24 hours to 2-24 hours**

The Applicant proposes to change the time to expulsion described in the labeling from 4-24 hours to 2-24 hours post misoprostol to more accurately reflect the data and real-life experiences with the drug. The Applicant reasons that in the large US trial upon

<sup>78</sup> Horning EL, Chen BA, Meyn LA, Creinin MD. Comparison of medical abortion follow-up with serum human chorionic gonadotropin testing and in-office assessment. Contraception 2012;85:402-407.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

which labeling is based (Spitz, 1998<sup>26</sup>), the median time to expulsion was 4 hours. Indeed, in that study, women were observed for several hours after misoprostol administration, and during the four hours of observation, 49% of the women expelled the products of conception, and 60% had by the fifth hour. Several studies are provided to corroborate this. Only one uses buccal misoprostol; however, the misoprostol was administered within 5 minutes of the Mifeprex, not at the 24-48 hour interval as proposed in this supplement. Nonetheless, in this trial, Lohr<sup>79</sup> found the median time to onset of cramping to be 2 hours (range 10 minutes to 13 hours) and bleeding to be 3 hours (range 9 minutes to 11 hours). This shorter duration to expulsion is also seen in several other pilot studies submitted where subjects took vaginal misoprostol immediately or within 6-8 hours of mifepristone. If the focus is shifted to the randomized controlled studies that report times to onset of bleeding and cramping and include vaginal misoprostol, we find data confirming the timing of expulsion in the 2-24 hour window proposed by the Applicant. Creinin<sup>25</sup> noted a median time to onset of cramping of 1.7 hours and to onset of bleeding of 2 hours after misoprostol (administered 24 hours after Mifeprex). In a similar study<sup>80</sup> comparing misoprostol administered 24 vs. 6-8 hours after Mifeprex, the median time to onset of cramping was 1.5 hours and to bleeding was 2 hours in women with misoprostol given 24 hours after Mifeprex.

**Reviewer comment:**

**The data from vaginal and buccal administration of misoprostol around 24 hours after mifepristone support the assertion that bleeding and cramping begin before the 4 hour mark that is currently labeled. Therefore the label should be revised to make this clearer. Median times seem to be around 1.5 to 2 hours. It is reasonable to label the time to expulsion 2-24 hours, but it could be labeled as beginning even earlier. A clearer label will help providers better counsel patients and patients can better select an appropriate time frame within the 24-48 hour window to take their misoprostol and can be prepared when the expulsion starts.**

**Reviewer's Final Recommendation:**

**Based on the available evidence, it is acceptable to revise the label so that it notes that the time to expulsion after misoprostol dosing is 2-24 hours.**

**2. Use of the term “ (b) (4) ”**

The Applicant proposes to use the term “ (b) (4) ” in place of all other terms in labeling and in the REMS materials, for consistency and (b) (4).  
The Applicant

<sup>79</sup> Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD. Oral mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study. *Contraception* 2007;76:215-220.

<sup>80</sup> 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.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

submitted an article demonstrating that nurse practitioners, certified nurse midwives and physician assistants can safely provide aspiration abortion.<sup>81</sup> The Division asked the Applicant to provide articles specifically addressing the provision of medical abortion services by non-physician practitioners, since that is the issue at hand.

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies took place in varying settings (urban, rural, international, low resource). The efficacy results are discussed in Section 6.1.10.

Regarding the safety of medical abortion provided by non-physician health care providers, a systematic review by Renner<sup>82</sup> identified five studies with a total of 8,908 subjects. A RCT in Nepal included 1,104 of those subjects, comparing medical abortions by nurses or auxiliary nurse midwives with those offered by physicians. Outcome data on 1,077 women showed no serious complications (hemorrhage requiring transfusion or condition necessitating hospitalization) and the rate of ongoing pregnancy or incomplete abortion did not vary by physician versus midlevel provider. Also in Nepal, Puri et al<sup>83</sup> described training female community health volunteers to provide education, and training auxiliary nurse midwives to provide medical abortion in intervention districts, and compared knowledge and medical abortion outcomes with those in neighboring districts where there were no interventions. Medical abortions were performed on 307 women in the intervention areas and 289 women in the comparison areas. There were five incomplete abortions (1.6%) in the intervention areas, treated with manual vacuum aspiration by the auxiliary nurse midwives, and 7 (2.4%) incomplete abortions in the comparison areas. The difference was not statistically significant. Kopp Kallner<sup>84</sup> conducted a randomized controlled equivalence trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. The trial showed fewer complications for the nurse midwife group, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, p=0.14).

---

<sup>81</sup> Weitz TA, Taylor D, Desai S, Upadhyay UD, Waldman J, Battistelli MF, Drey EA. Safety of aspiration abortion performed by nurse practitioners, certified nurse midwives, and physician assistants under a California legal waiver. *Am J Public Health* 2013;103:454-461.

<sup>82</sup> Renner R-M, Brahma D, Kapp N. Who can provide effective and safe termination of pregnancy care: a systematic review. *BJOG* 2013;10:23-31.

<sup>83</sup> Puri M, Tamang A, Shrestha P, Joshi D. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. *Reproductive Health Matters* 2015;Suppl(44):94-103.

<sup>84</sup> Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell-Danielsson K. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomized controlled equivalence trial. *BJOG* 2015;122:510-517.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

There were no serious complications and no blood transfusions in the study. There was no difference in unscheduled visits. Nurse midwives did call for more second opinions (26%) versus doctors (4%). Olavarrieta<sup>85</sup> conducted a randomized controlled non-inferiority trial in Mexico City abortion clinics. Eight physicians and seven nurses who had not previously independently provided medical abortion care received 1.5 weeks of training. A total of 1,088 women were randomized to two groups of providers. Nurses were not found to be inferior to physicians in the provision of abortion care. There was only one serious adverse event in the physician group, a woman requiring admission and surgical aspiration for heavy bleeding. Nurses requested consultation with an experienced obstetrician in 9 cases, whereas physicians requested consultation only twice.

#### **Reviewer Comments:**

**The Applicant provided data from over 3,200 women in randomized controlled trials and data on 596 women in prospective cohorts comparing medical abortion care by physicians versus nurses or nurse midwives. The studies were conducted in varying settings (international, urban, rural, low-resource) and found no differences in efficacy, serious adverse events, ongoing pregnancy or incomplete abortion between the groups. Two studies did show that nurses or nurse midwives called for more second opinions than physicians, but these numbers were a small portion of the total subjects included.**

**Midlevel providers in the United States, such as nurse practitioners, nurse midwives and physician assistants currently provide family planning services and abortion care, including medical abortion care, under the supervision of physicians. The data here demonstrate that it would be safe to allow healthcare providers who are licensed to prescribe medications and who meet the criteria in the REMS to become certified to provide medical abortion care with Mifeprax and misoprostol. Midlevel providers are already practicing abortion care under the supervision of physicians, and the approved labeling and the REMS Prescriber's Agreement already stipulate that prescribers must be able to refer patients for additional care, including surgical management if needed. Therefore, facilities that employ midlevel prescribers already have an infrastructure in place for consultation and referral.**

#### **Reviewer's Final Recommendation:**

**Based on the available evidence, it is safe for midlevel providers to administer medical abortion. The term in the revised Prescriber Agreement Form will be "a healthcare provider who prescribes." Per the review by the (b) (6) (b) (6) dated March 29, 2016, this term provides an accurate**

<sup>85</sup> Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousiequez 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.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

**representation of the varied practitioners who are prescribers, while at the same time using language that is consistent with statute. We concur with the review.**

### **3. Removal of references to “Under Federal Law” from the Prescriber’s Agreement**

The Applicant requests removal of the phrase “under Federal law” from the Prescriber’s Agreement portion of the REMS materials. The phrase appears in two places:

- “Under Federal law, Mifeprex must be provided by or under the supervision of a licensed physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately.
  - Ability to diagnose ectopic pregnancies.
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.”
- “Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss them, obtain her signature on the Patient Agreement, and sign it yourself.”

The Applicant rationalizes that all of the conditions of Mifeprex approval, including the REMS, are under Federal law and that the statement is redundant and are no more subject to Federal law than the other conditions of approval.

#### **Reviewer comment:**

**A rationale for the original inclusion of the phrase “Under Federal law” cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and can be removed from the Prescriber’s Agreement.**

#### **Reviewer’s Final Recommendation:**

**The term “under Federal law” can be removed from the Prescriber’s Agreement.**

### **4. Addition of misoprostol to the indication statement**

The Indication and Usage section of the currently approved labeling is as follows:

“Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days’ pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination.

Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 mcg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS)."

The Applicant proposed two alternative indication statements, both of which include reference to misoprostol:

(b) (4)

Or

(b) (4)

The Applicant provides the rationale that:

- the two drugs are used in combination and placing misoprostol in the indication statement early on in labeling gives it greater prominence and highlights the importance of completing the full treatment regimen

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

- the mention of misoprostol enhances the goal of labeling, which is to give healthcare providers information necessary for safe and effective use of Mifeprex.

Subsequently on February 25, 2016, the Applicant proposed (b) (4) (b) (4) gestational age through 70 days, based on the literature already submitted.

**Reviewer comment:**

**We recommend that the Indication Statement read:**

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

**The rationale for this is that:**

- **All supporting data are based on the combined regimen**
- **Inclusion of misoprostol in the Indication Statement would be consistent with the rest of Mifeprex labeling and with current medical practice**
- **It would be consistent with current FDA thinking (e.g., the internal Label Review Tool) which states that the indication and use statement should include “Information if drug is to be used only in conjunction with another therapy.”**

**Reviewer’s Final Recommendation:**

**Misoprostol should be included in the Indication Statement for Mifeprex.**

## **8 Postmarket Experience**

A comprehensive review of the adverse events associated with Mifeprex from September 28, 2000 through November 17, 2015, performed by (b) (6), (b) (6), yielded the following information on reported deaths. Regarding the US cases, there were 17 reported deaths. Deaths were associated with sepsis in eight of the 17 (seven cases tested positive for *Clostridium sordellii*, one case tested positive for *Clostridium perfringens*). Seven of the eight fatal sepsis cases reported vaginal misoprostol use; one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a case of delayed onset toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. The autopsy report on the ninth death became available to the Agency and was reviewed on December 2, 2015. It showed the woman died of pulmonary emphysema.

There were 11 additional deaths in women in foreign countries who used mifepristone for medical termination of pregnancy. These fatal cases were associated with the

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

following: sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial; sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; “multivisceral failure;” thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes, a jejunostomy feeding tube, and severe cystic fibrosis; and a case of *Clostridium sordellii* sepsis (from a published literature report).

**Reviewer Comments:**

**While an exact rate of death with use of mifepristone cannot be calculated from this information, given that there have been over 2.5 million uses of Mifeprex by US women since its marketing in 2000, the number of deaths is very low. Moreover, half of the deaths were associated with *C. sordellii* sepsis. Seven out of 8 of these cases occurred in women who used misoprostol via the vaginal route while one used buccal misoprostol. Since at least 2006, PPFA (comprising the majority of US medical abortion providers) switched its national guidelines to avoid vaginal administration of misoprostol (even though the data did not find a causal relationship).<sup>23</sup> Although the possibility that Mifeprex might increase the likelihood of infection by adversely affecting immune system function has been raised, the overall event rate of serious infections does not support this.**

**Since 2009, there have been no *C. sordellii* deaths associated with medical abortion in the US. This reviewer finds that the postmarketing data on deaths associated with medical abortion demonstrate low numbers and an improved safety profile with the buccal route of misoprostol administration as compared with the vaginal route.**

**The review by (b) (6) (b) (6) also yielded the following**

Table 21 summarizing hospitalizations, blood loss requiring transfusions, and severe infections.

**Table 21: US Postmarketing AEs- Mifepristone for Medical Abortion**

Date ranges of reports received	09/28/00 <sup>†</sup> -10/31/12	11/1/12 - 04/30/14 <sup>‡</sup>
Cases with any adverse event	2740	504
Hospitalized, excluding deaths	768	110
*Experienced blood loss requiring transfusions <sup>§</sup>	416	66
Infections <sup>  </sup> (*Severe infections <sup>¶</sup> )	308 (57)	37 (5)



## Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

U.S. approval date.  
 † FDA implemented FAERS on September 10, 2012, and migrated all of the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. As a result of this change, it is not recommended to calculate a cumulative number when reviewing the data provided in Table 5.  
 \* The majority of these women are included in the hospitalized category in Table 5.  
 § As stated in the approved Mifeprax (mifepristone) labeling, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days. Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.  
 ¶ This category includes endometritis (inflammation resulting from an infection involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as chlamydia and gonorrhea, cystitis, and toxic shock syndrome not associated with a pelvic infection.  
 ¶ This subset of infections includes cases that were determined to be severe based on medical review of the available case details. Severe infections generally result in death or hospitalization for at least 2-3 days, require intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, or have other physical or clinical findings, laboratory data, or surgery that suggest a severe infection.

Source: Review by (b) (6) (b) (6) (b) (6) dated 08/27/2015.

The (b) (6) review also describes ectopic pregnancies:

**Table 22: US Postmarketing Ectopic Cases- Mifepristone for Medical Abortion**

Date Range of Cumulative Reports	9/28/2000-10/31/14*	11/1/14-4/30/2015
Ectopic Pregnancies†	79	10

\* U.S. approval date

† Administration of mifepristone and misoprostol is contraindicated in patients with confirmed or suspected ectopic pregnancy (a pregnancy outside the uterus).

Source: (b) (6) (b) (6) (b) (6) Mifepristone U.S. Post-marketing Adverse Events 6 month Update Summary through 04/30/2015, dated 08/20/2015.

**Reviewer comment:**

**While exact rates cannot be calculated, as these reports are spontaneously generated, a few conclusions can be drawn from the information provided:**

- **Given that there have been over 2.5 million uses of Mifeprax by US women since its marketing in 2000, including the use of the proposed dosing regimen and extended gestational age at many clinic/office sites, the numbers of hospitalizations, severe infections, blood loss requiring transfusion and ectopic pregnancy will likely remain acceptably low.**
- **The numbers of each of these adverse events appears to have remained steady over time, with a possible decrease in severe infections.**

A discussion of a (b) (6) review of uterine rupture is found in the Section Significant Adverse Events.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

(b) (6) identified another safety signal in a review dated January 27, 2016. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. A literature search did not reveal any case reports of either adverse event with mifepristone. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of the various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema.

In the case of anaphylaxis, it was reported that the patient experienced an anaphylactic reaction three hours after mifepristone administration; however, co-administration of doxycycline was also documented. Because both mifepristone and doxycycline were discontinued simultaneously, the exact cause of the anaphylactic reaction cannot be determined.

Regarding angioedema, five of the six cases noted a time-to-onset within 24 hours of mifepristone administration for the termination of pregnancy, with no additional suspect medications reported. The remaining case of angioedema with mifepristone reported a time-to-onset of approximately one week in a Cushing's syndrome patient with a complex medical history and multiple concomitant medications; however, this case noted both a positive dechallenge and rechallenge upon sole re-introduction of mifepristone therapy. Evaluation of these FAERS cases provides supportive evidence of a drug-event association between angioedema and mifepristone. The (b) (6) reviewer recommends the inclusion of anaphylaxis and angioedema within the Mifeprex labeling, specifically to the Contraindications and Adverse Reactions Postmarketing Experience sections.

**Reviewer Comment:**

**There does appear to be an association with angioedema and mifepristone administration. The reviewers agree with inclusion of anaphylaxis and angioedema in the labeling for Mifeprex and with continued pharmacovigilance for anaphylaxis.**

## **9 Appendices**

### **9.1 Literature Review/References**

This NDA review obviously involved an extensive review of resources and the peer-reviewed medical literature that was pertinent to the requested changes of the Applicant. Such sources are noted throughout the review in footnotes. A detailed Reference List is found in Appendix 9.6.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

## 9.2 Labeling Recommendations

The package insert (PI) for this product was submitted in the Physician Labeling Rule (PLR) format. Although not required for this supplement, Section 8 was revised in accord with the Pregnancy and Lactation Labeling Rule (PLLR). Section 17 Patient Counseling Information was also revised to be compatible with the new dosing regimen and follow-up. Major changes were made that updated the labeling with new safety and efficacy information, especially in two areas:

- 1) 6.1 Clinical Trials Experience in the section 6 Adverse Reactions
- 2) 14 Clinical Studies

Changes were also made in the patient package insert (PPI) and Medication Guide for the product. These format and content updates marked a significant improvement in the label. Agreement on the Final Approved label was reached with the Applicant on March 29, 2016.

### Reviewer comment:

**The new dosing regimen was based on the extensive number of articles submitted by the Applicant from the peer reviewed medical literature. The revised label used the new PLR format which is a complete change from the previous style. This meant that the newly approved label was extensively rewritten and much improved from the old format.**

## 9.3 Advisory Committee Meeting

An Advisory Committee met in 1996 to discuss the approval of mifepristone plus misoprostol for medical termination of early pregnancy. There has been extensive US (15+ years with over 2.5 million uses) and global use (27+ years) of mifepristone and misoprostol for the medical termination of early pregnancy. No special external consultations were requested by the review Divisions. The FDA determined that the efficacy supplement did not raise complex scientific or other issues that would warrant holding an advisory committee meeting before approval of the supplement.

## 9.4 (b) (6) ( (b) (6) Meeting

As noted in Product Regulatory Information, Mifeprex was originally approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, in accordance with § 314.520 of subpart H, FDA restricted the distribution of Mifeprex and required that Mifeprex be provided by or under the supervision of a physician who met certain qualifications. Further, practitioners had to complete a Prescriber's Agreement, provide patients with a Medication Guide and have patients sign a Patient Agreement. Mifeprex was included on the list of products deemed to have in effect an approved REMS<sup>86</sup> under section

---

86 Federal Register / Vol. 73, No. 60 | Issued: March 27, 2008



## Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of FDA Amendments Act (FDAAA) of 2007. A formal REMS proposal was submitted by Danco and approved on June 8, 2011, with the essential elements unchanged. The REMS included:

- Medication Guide
- Elements to Assure Safe Use (ETASU):
  - Prescribed only by certified prescribers (ETASU A; includes a Prescriber's Agreement)
  - Dispensed only in certain healthcare settings (ETASU C)
  - Dispensed with documentation of safe use conditions (ETASU D; includes a Patient Agreement)
- Implementation System
  - Distributed only by certified distributors

Following this approval, two REMS assessment reports were completed. The Year 1 assessment was completed on June 1, 2012 and the Years 2-4 assessment was completed on June 2, 2015. Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

On July 16, 2015, the Applicant submitted a revised REMS as part of the efficacy supplement. The proposed modifications included:

- Prescriber's Agreement Form
  - Remove "Under Federal law"
  - Replace "physician" with "(b) (4)"

The Agency determined that broader review of the REMS was warranted concurrently with the efficacy supplement because some proposed changes in labeling dovetail with proposed changes to the REMS, and the documents should remain consistent with each other. Further, extensive review of the postmarketing experience based on the literature submitted to support the efficacy supplement, and pharmacovigilance, suggested that certain components of the REMS may no longer be necessary to assure safe use of Mifeprex.

In light of the efficacy review, upon assessment of the proposed modifications, (b) (6) concurs with (b) (6) recommendations that:

- Removal of "under Federal law" from the Prescribers' Agreement was acceptable (see discussion in Additional Submissions / Issues)
- The term "healthcare providers who prescribe" is preferable to (b) (4) (see discussion in Additional Submissions / Issues)

(b) (6) and (b) (6) also proposed the following modifications:

- Removal of the Medication Guide from the REMS (will remain a part of labeling and must be distributed by the prescriber as required under 21 CFR part 208)
- Removal of the Patient Agreement form - Documentation of Safe Use (ETASU D)

## Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

- Revision of the Prescriber's Agreement form
- Revision of the REMS goal to reflect above changes

FDA considered the need for the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." FDA has received such reports for 15 years; the safety profile of Mifeprex is well-characterized, no new safety concerns have arisen in recent years, and the known serious risks occur rarely. For this reason, the reviewers do not believe ongoing reporting of all of the specified adverse events is warranted. The Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience.

(b) (6) and (b) (6) met with the (b) (6) ( (b) (6) on January 15, 2015, to discuss the proposed modifications. The (b) (6) concurred with the removal of the term "under Federal law" and with use of the term "healthcare providers who prescribe." The (b) (6) also concurred with the removal of the Medication Guide (MG) from the REMS, though the document would remain a part of labeling. FDA has been maintaining MGs as labeling but removing them from REMS when, as here, inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks, such as when the MG is redundant and not providing additional use or information to the patient about the risk(s) the REMS is intended to mitigate. This is consistent with ongoing efforts to streamline REMS by allowing for updates to the MG without need for a REMS modification. (b) (6) and the (b) (6) had subsequent interactions and on February 23, 2016, the (b) (6) concurred with the decision to remove the Patient Agreement (ETASU D) from the REMS. This decision was based on the following rationale:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance
- Established clinical practice includes patient counseling and documentation of Informed Consent, and, more specifically with Mifeprex, includes counseling on all options for termination of pregnancy, access to pain management and emergency services if needed. The National Abortion Federation (NAF) provides clinical practice guidelines<sup>Error! Bookmark not defined.</sup> and evidence shows that practitioners are providing appropriate patient counseling and education; a survey published in 2009 demonstrated that 99% of facilities surveyed provided pre-abortion counseling with patient education.<sup>87</sup> This indicates that the Patient Agreement form is duplicative and no longer necessary to ensure that the benefits of the drug outweigh the risks.

APPEARS THIS  
 WAY ON  
 ORIGINAL

<sup>87</sup> 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.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines cover the safety information that is duplicated in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the supervision of a certified prescriber at the time the patient receives treatment with Mifeprex.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

APPEARS THIS WAY ON ORIGINAL



Clinical Review

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

NDA 020687/S-020- Mifeprex

**9.4 Abbreviations****List of Abbreviations**

<b>Abbreviation</b>	<b>Term</b>
<b>ACOG</b>	American College of Obstetrics and Gynecology
<b>APHA</b>	American Public Health Association
<b>CDER</b>	Center for Drug Evaluable and Research
<b>CDRH</b>	Center for Devices and Radiological Health
(b) (6)	(b) (6)
<b>FU</b>	follow up
<b>GA</b>	gestational age
<b>IRB</b>	Institutional Review Board
<b>LFU</b>	lost to follow up
<b>LMP</b>	last menstrual period
<b>MAB</b>	medical abortion
<b>MG</b>	Medication Guide
<b>Miso</b>	misoprostol
<b>NA</b>	not applicable
<b>NAF</b>	National Abortion Federation
<b>NDA</b>	New drug application
<b>NR</b>	not reported
<b>NSAID</b>	non-steroidal anti-inflammatory drug
<b>PPFA</b>	Planned Parenthood Federation of America
<b>PREA</b>	Pediatric Research Equity Act
<b>REMS</b>	Risk Evaluation and Mitigation Strategies
<b>ROA</b>	route of administration
(b) (6)	(b) (6)
<b>SAB</b>	surgical abortion
<b>WHO</b>	World Health Organization

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

## 9.5 List of References

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

Alam A, Bracken H, et al. Acceptability and Feasibility of Mifepristone-Misoprostol for Menstrual Regulation in Bangladesh. *International Persp on Sexual and Reprod Health* 2013;39(2):79-87.

American College of Obstetricians and Gynecologists. Practice bulletin No. 143: medical management of first-trimester abortion. *Obstet Gynecol* 2014;123(3):676-92. doi:10.1097/01.AOG.0000444454.67279.7d.

Bartz B and Goldberg A. Medical Abortion. *Clin Obstet and Gyn* 2009;52:140-50.

Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, Amar E, Descotes J, Vial T. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. *BJOG* 2013;120:568–575.

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.

Blum J, Raghavan S, Dabash R, Ngoc NTN, Chelli H, Hajri S, Conkling K, Winikoff B. comparison of misoprostol-only and combined mifepristone-misoprostol regimens for home-based early medical abortion in Tunisia and Vietnam. *Int J Gynecol Obstet* 2012;118:166-171.

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.

Bracken H, Dabash R, Tsertsvadze G, et al. A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial. *Contraception* 2014;89(3):181-6.

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

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.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

Chai J, Wong CY, Ho PC. A randomized clinical trial comparing the short-term side effects of sublingual and buccal routes of misoprostol administration for medical abortions up to 63 days' gestation. *Contraception* 2013;87:480-5.

Chen BA, Reeves MF, Creinin MD, Gilles JM, Barnhart K, Westhoff C, Zhang J. National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial. *Am J Obstet Gynecol* 2008;198(6):626.d1-5 doi: 10.1016/j.ajog.2007.11.045. Epub 2008 Feb 15.

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

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.

Chong E, Frye LJ, Castle J, Dean G, Kuehl L, Winikoff B. A prospective, non-randomized study of home use of mifepristone for medical abortion in the US. *Contraception* 2015;92:215-291.

Cleland K, Smith N. Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data. *Contraception* 2015;92:179-81.

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.

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.

Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Medical Abortion at the Same Time (MAST Study Trial Group). Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion a randomized controlled trial. *Obstet Gynecol* 2007;109:885-894.

Dahiya K, Ahuja K, Dhingra A, et al. Efficacy and safety of mifepristone and buccal misoprostol versus buccal misoprostol alone for medical abortion. *Arch Gynecol Obstet* 2012;285:1055-8.

Dehlendorf CE, et al. Medication abortion failure in women with and without previous cesarean section. *Contraception* 2015 92:463-68.



(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

Faundes A. The combination of mifepristone and misoprostol for the termination of pregnancy. *Int J Gynecol Obstet* 2011;115:1-4.

FDA label for ella:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/022474s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf)

FDA Label for Korlym:

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/202107s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202107s000lbl.pdf)

FDA label for Mifeprex:

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2000/20687lbl.htm](http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.htm)

Fiala C, Safar P, Bygdeman M, Gemzell-Danielsson K. Verifying the effectiveness of medical abortion; ultrasound versus hCG testing. *Eur J Obstet Gynecol Reprod Biol* 2003;109:190-195.

Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with prostaglandin analogue. *Contraception* 2006;74:66-86.

Fjerstad M. Figuring out follow-up. *Mife Matters*. Planned Parenthood Federation of America/Coalition of Abortion Providers 2006;13:2-3.

Fjerstad M, Sivin I, Lichtenberg ES, Trussell J, Cleland K, Cullins V. Effectiveness of medical abortion with mifepristone and buccal misoprostol through 59 gestational days. *Contraception* 2009;80:282-6.

Fjerstad M, Trussell J, et al. Rates of serious infection after changes in regimens for medical abortion. *NEJM* 2009;361:145-51.

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.

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.

Gautam R, Agrawal V. Early medical termination pregnancy with methotrexate and misoprostol in lower segment cesarean section cases. *J Obetet Gynaecol Res*. 2003; 29(4):251-256.

Giri A, Tuladhar H, et al. Prospective study of medical abortion in Nepal Medical College- a one year experience. *Nepal Medical Coll J* 2011;13(3):213-15.

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

Gold M, Chong E. If we can do it for misoprostol, why not for mifepristone? The case for taking mifepristone out of the office in medical abortion. *Contraception* 2015;92:194-196.

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.

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

Grossman D, Grindlay K. Alternatives to ultrasound for follow-up after medication abortion: a systematic review. *Contraception* 2011;83:504-510.

Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.

Gynuity website, [www.gynuity.org](http://www.gynuity.org), Medical Abortion in Developing Countries- List of Approvals.

Harrison P. Medicine Control Agency background communication to the FDA. June 14, 2001.

Horning EL, Chen BA, Meyn LA, Creinin MD. Comparison of medical abortion follow-up with serum human chorionic gonadotropin testing and in-office assessment. *Contraception* 2012;85:402-407.

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.

Jwarah E, Greenhalf JO. Rupture of the uterus after 800 micrograms misoprostol given vaginally for termination of pregnancy. *BJOG* 2000;107:807.

Jones RK, Jerman J. Abortion incidence and service availability in the United States, 2011. *Perspectives on Sexual and Reproductive Health* 2014;46(1):3-14. doi10.1363/46e0414.

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.

Kim JO, et al. Oral misoprostol and uterine rupture in the first trimester of pregnancy: A case report. *Reproductive Toxicology* 2005;20:575-577.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

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.

Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell-Danielsson K. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomized controlled equivalence trial. *BJOG* 2015;122:510-517.

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

Løkeland M, Iversen OE, Engeland A, Økland I. Medical abortion with mifepristone and home administration of misoprostol up to 63 days' gestation. *Acta Obstet Gynecol Scand* 2014;93:647-653.

Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD. Oral mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study. *Contraception* 2007;76:215-220.

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.

Lynd K, Blum J, Ngoc NTN, Shochet T, Blumenthal PD, Winikoff B. Simplified medical abortion using a semi-quantitative pregnancy test for home-based follow-up. *Int J Gynecol Obstet* 2013;121:144-148.

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.

Mifegyne Summary of Product Characteristics. Exelgyn Laboratories- June 2013.  
<https://www.medicines.org.uk/emc/medicine/617>

National Abortion Federation Guidelines 2015. <http://prochoice.org/resources/clinical-policy-guidelines/>

Ngo TD, Park MH, Xiao Y. Comparing the WHO versus China recommended protocol for first trimester medical abortion: a retrospective analysis. *Int J Womens Health* 2012;4:123-7.

Ngoc NTN, et al. Comparing two early medical abortion regimens: mifepristone+misoprostol vs. misoprostol alone. *Contraception* 2011;83:410-17.



Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprax

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.

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.

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.

Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousiequez 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.

Pazol K, Creanga AA, Burley KD, Jamieson DJ. Abortion surveillance - United States, 2011. *MMWR Surveill Summ* 2014;63:1-41.

Pazol K, Creanga AA, Zane SB, Burley KD, Jamieson DJ. Abortion surveillance--United States, Centers for Disease Control and Prevention (CDC). *MMWR Surveill Summ* 2012;61(SS-8):1-44 and *Surveillance Summaries* Nov 27, 2015;64(SS10):1-40.

Pena M, Dzuba IG, Smith PS, et al. Efficacy and acceptability of a mifepristone-misoprostol combined regimen for early induced abortion among women in Mexico City. *Int J Gynaecol Obstet* 2014;127:82-5.

Perriera LK, Reeves MF, Chen BA, Hohmann HL, Hayes J, Creinin MD. Feasibility of telephone follow-up after medical abortion. *Contraception* 2010;81:143-149.

Phelps RH, et al. Mifepristone abortion in minors. *Contraception* 2001;64:339-343.

Pons JC, Papiernik E. Mifepristone teratogenicity. *Lancet* 1991;338(8778):1332-3.

Puri M, Tamang A, Shrestha P, Joshi D. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. *Reproductive Health Matters* 2015;Suppl(44):94-103.

Raghavan S, et al. Comparison of 400 mcg buccal and 400 mcg sublingual misoprostol after mifepristone medical abortion through 63 days' LMP: a randomized controlled trial. *Contraception* 2010;82:513-9.

Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87:26-37.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

Renner R-M, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care/ A systematic review. *BJOG* 2013;10:23-31.

Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7. 3rd ed. London (UK): RCOG Press; 2011.

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.

Sedgh G, et al. Induced abortion: incidence and trends worldwide from 1995 to 2008. *Lancet*, 2012;379:625-32.

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.

Spitz IM, et al. Early Pregnancy Termination with Mifepristone and Misoprostol in the United States. *NEJM* 1998;338(18):1241-47.

Spitz IM. Mifepristone: where do we come from and where are we going? *Clinical development over a quarter of a century. Contraception* 2010;82:442–52.

Swica Y, et al. Acceptability of home use of mifepristone for medical abortion. *Contraception* 2013;88:122-127.

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.

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.

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.

Weitz TA, Taylor D, Desai S, Upadhyay UD, Waldman J, Battistelli MF, Drey EA. Safety of aspiration abortion performed by nurse practitioners, certified nurse midwives, and physician assistants under a California legal waiver. *Am J Public Health* 2013;103:454-461.

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

Wiegerinck MMJ, Jones HE, O'Connell, K, Lichtenberg ES, Paul M, Westhoff CL. Medical abortion practices: a survey of National Abortion Federation members in the United States. *Contraception* 2008;78:486-491.

Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. *BJOG* 2008;115:1575-77.

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.

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.

World Health Organization April 2015 Model Lists of Essential Medicines Available online at <http://www.who.int/medicines/publications/essentialmedicines/en/>

APPEARS THIS WAY ON ORIGINAL



Clinical Review

(b) (6) and (b) (6)  
 NDA 020687/S-020- Mifeprex

<b>9.6 Mifepristone Approvals Globally</b>	2003		2015
	<input type="checkbox"/>	<b>Estonia</b>	<input type="checkbox"/> Canada
<b>1988</b>	2004		
	<input type="checkbox"/>	Guyana	
<input type="checkbox"/> China	<input type="checkbox"/>	Moldova	
<input type="checkbox"/> France	2005		
1991-	<input type="checkbox"/>	Albania	
<input type="checkbox"/> UK	<input type="checkbox"/>	Hungary	
1992	<input type="checkbox"/>	Mongolia	
<input type="checkbox"/> Sweden	<input type="checkbox"/>	Uzbekistan	
1999	2006		
<input type="checkbox"/> Austria	<input type="checkbox"/>	Kazakhstan	
<input type="checkbox"/> Belgium	2007		
<input type="checkbox"/> Denmark	<input type="checkbox"/>	Armenia	
<input type="checkbox"/> Finland	<input type="checkbox"/>	Kyrgyzstan	
<input type="checkbox"/> Germany	<input type="checkbox"/>	Portugal	
<input type="checkbox"/> Greece	<input type="checkbox"/>	Tajikistan	
<input type="checkbox"/> Iceland	2008		
<input type="checkbox"/> Israel	<input type="checkbox"/>	Nepal	
<input type="checkbox"/> Luxembourg	<input type="checkbox"/>	Romania	
<input type="checkbox"/> Netherlands	2009		
<input type="checkbox"/> Russia	<input type="checkbox"/>	Cambodia	
<input type="checkbox"/> Spain	<input type="checkbox"/>	Italy	
<input type="checkbox"/> Switzerland	2010		
2000	<input type="checkbox"/>	Zambia	
<input type="checkbox"/> Norway	<input type="checkbox"/>	Ghana	
<input type="checkbox"/> Taiwan	<input type="checkbox"/>	Mexico	
<input type="checkbox"/> Tunisia	<input type="checkbox"/>	Mozambique	
<input type="checkbox"/> US	2012		
2001	<input type="checkbox"/>	Australia	
<input type="checkbox"/> New Zealand	<input type="checkbox"/>	Bangladesh	
<input type="checkbox"/> South Africa	<input type="checkbox"/>	Ethiopia	
<input type="checkbox"/> Ukraine	<input type="checkbox"/>	Kenya	
2002	2013		
<input type="checkbox"/> Belarus	<input type="checkbox"/>	Azerbaijan	
<input type="checkbox"/> Georgia	<input type="checkbox"/>	Bulgaria	
<input type="checkbox"/> India	<input type="checkbox"/>	Czech Republic	
<input type="checkbox"/> Latvia	<input type="checkbox"/>	Slovenia	
<input type="checkbox"/> Serbia	<input type="checkbox"/>	Uganda	
<input type="checkbox"/> Vietnam	<input type="checkbox"/>	Uruguay	
	2014		
	<input type="checkbox"/>	Thailand	

Clinical Review

(b) (6) and (b) (6)  
NDA 020687/S-020- Mifeprex

APPEARS THIS WAY ON ORIGINAL

---

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

---

/s/

---

(b) (6)  
03/29/2016

(b) (6)  
03/29/2016

(b) (6)  
03/29/2016

I concur with (b) (6) conclusions and recommendations for approval of this efficacy supplement.



Case 2:22-cv-00223-Z Document 28-1 Filed 01/13/23 Page 107 of 286 PageID 2171  
**CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement**

**NDA/BLA Number:** 020687      **Applicant:** Danco Labs      **Stamp Date:** May 29, 2015  
**Drug Name:** Mifeprax (Mifepristone)      **NDA/BLA Type:** supplement #020

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			Paper submission.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?			x	
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?		x		The applicant has not provided module 2 summaries as this is an NDA based on published literature. The applicant has provided a justification summarizing the evidence of safety and efficacy for the proposed changes.
9.	Has the applicant submitted the integrated summary of safety (ISS)?		x		See comment for 8.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		x		See comment for 8.
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Scientific justification-30 pg document
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	x			(b) (2)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	x			The sponsor provides a bridge from the approved product to the proposed changes, with literature based

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908



	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
					transfusion, infection requiring IV antibiotics, death). There are another 5 articles with limited safety information and 6 articles with safety information, but using different dosing regimens (e.g. not the approved or proposed new regimen).
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			x	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			x	There is no mapping of investigator terms to preferred terms. AE's were variably ascertained; 21 studies include data on SAE's of interest, 7 have limited safety information, 6 have safety information on the approved dosing regimen. Some 7 studies report no safety information.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	As of 7/16/15, there is one reported death; a complete report will be forthcoming. This

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908



Case 2:22-cv-00223-Z Document 28-1 Filed 01/13/23 Page 110 of 286 PageID 2174  
**CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement**

	Content Parameter	Yes	No	NA	Comment
					is not part of the presently submitted application.
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			The applicant requested a partial waiver for patients <12 and a waiver for patients 12-17, based on data from one study which included 322 subjects <17 years old.
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	29/46 studies are US data, 17 are based on foreign data.
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	NDA relies upon published studies; datasets were not provided.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
37.	Are all datasets to support the critical safety analyses available and complete?			x	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	NDA relies upon published studies; CRFs were not provided.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?			X	
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an			x	

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

**CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	IRB and with adequate informed consent procedures?				

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** \_\_\_yes\_\_\_

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There is one review issue which will need to be addressed.  
 The proposed label contains information from the original studies and not from the studies supporting the new dosing regimen and the other proposed changes (e.g., including healthcare providers prescribing Mifeprex and home use of misoprostol). The Sponsor will need to update the proposed label.

(b) (6)	7/16/15
Reviewing Medical Officers	Date
(b) (6)	7/16/15
	Date

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

---

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

---

/s/

---

(b) (6)  
07/16/2015

(b) (6)  
07/17/2015

(b) (6)  
07/17/2015



**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX® (mifepristone) tablets, for oral use  
Initial U.S. Approval: 2000

**WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING**

See full prescribing information for complete boxed warning. Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)
- Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)

MIFEPREX is only available through a restricted program called the mifepristone REMS Program (5.3). Before prescribing MIFEPREX, inform the patient about these risks. Ensure the patient knows whom to call and what to do if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

**INDICATIONS AND USAGE**

MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

**DOSAGE AND ADMINISTRATION**

- 200 mg MIFEPREX on Day 1, followed 24-48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

**DOSAGE FORMS AND STRENGTHS**

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

**CONTRAINDICATIONS**

- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

**WARNINGS AND PRECAUTIONS**

- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

**ADVERSE REACTIONS**

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or [medicaldirector@earlyoptionpill.com](mailto:medicaldirector@earlyoptionpill.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 01/2023

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING**

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
  - Dosing Regimen
  - Patient Management Following Misoprostol Administration
  - Post-treatment Assessment: Day 7 to 14
  - Contact for Consultation
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
  - Infections and Sepsis
  - Uterine Bleeding
  - Mifepristone REMS Program
  - Ectopic Pregnancy
  - Rhesus Immunization
- ADVERSE REACTIONS
  - Clinical Trials Experience
  - Postmarketing Experience
- DRUG INTERACTIONS
  - Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

- Drugs that May Increase Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)
- Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)
- USE IN SPECIFIC POPULATIONS
  - Pregnancy
  - Lactation
  - Pediatric Use
- OVERDOSAGE
- DESCRIPTION
- CLINICAL PHARMACOLOGY
  - Mechanism of Action
  - Pharmacodynamics
  - Pharmacokinetics
- NONCLINICAL TOXICOLOGY
  - Carcinogenesis, Mutagenesis, Impairment of Fertility
- CLINICAL STUDIES
- HOW SUPPLIED/STORAGE AND HANDLING
- PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### **WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING**

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection.** Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis [see *Warnings and Precautions (5.1)*].
- **Bleeding.** Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding [see *Warnings and Precautions (5.2)*].

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the mifepristone REMS Program [see *Warnings and Precautions (5.3)*].

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

## 1 INDICATIONS AND USAGE

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

Remove any intrauterine device (“IUD”) before treatment with MIFEPREX begins [see *Contraindications (4)*].

The dosing regimen for MIFEPREX and misoprostol is:

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
  - *Day One:* MIFEPREX Administration  
One 200 mg tablet of MIFEPREX is taken in a single oral dose.
  - *Day Two or Three:* Misoprostol Administration (minimum 24-hour interval between MIFEPREX and misoprostol)  
Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

**Figure 1**



**2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side**

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol [see *Clinical Studies (14)*], discuss with the patient an appropriate location for them to be when taking the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

## **2.2 Patient Management Following Misoprostol Administration**

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms [see *Adverse Reactions (6)*].

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if the patient has questions following the administration of the misoprostol
- The name and phone number of the healthcare provider who will be handling emergencies.



### 2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Patients should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, patients may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took MIFEPREX and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Patients who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion [see *Use in Specific Populations (8.1)*]. Advise the patient whether you will provide such care or will refer them to another provider as part of counseling prior to prescribing MIFEPREX.

### 2.4 Contact for Consultation

**For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).**

## 3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with "MF."

## 4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any of the following conditions:
  - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) [see *Warnings and Precautions (5.4)*]
  - Chronic adrenal failure (risk of acute adrenal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute adrenal insufficiency)
  - History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported [see *Adverse Reactions (6.2)*])
  - Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)

- Inherited porphyrias (risk of worsening or of precipitation of attacks)
- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device (“IUD”) in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX [see *Boxed Warning*]. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting, or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

### 5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications, and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion [see *Boxed Warning*].

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in patients who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

### 5.3 Mifepristone REMS Program

MIFEPREX is available only through a restricted program under a REMS called the mifepristone REMS Program, because of the risks of serious complications [see *Warnings and Precautions (5.1, 5.2)*].

Notable requirements of the mifepristone REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form.
- Patients must sign a Patient Agreement Form.
- MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.

Further information is available at 1-877-4 Early Option (1-877-432-7596).

### 5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies [see *Contraindications (4)*]. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Patients who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

### 5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

## 6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis [see *Warnings and Precautions (5.1)*]
- Uterine bleeding [see *Warnings and Precautions (5.2)*]

### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from U.S. studies, because rates reported in non-U.S. studies were markedly lower and are not likely generalizable to the U.S. population. In three U.S. clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label. Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.



About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors, including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most patients can expect bleeding more heavily than they do during a heavy menstrual period [see *Warnings and Precautions (5.2)*].

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

**Table 1**  
**Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies**

Adverse Reaction	# 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

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

**Table 2**  
**Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-U.S. Clinical Studies**

Adverse Reaction	U.S.			Non-U.S.		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported

\* This outcome represents a single patient who experienced death related to sepsis.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Infections and infestations:* post-abortal infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)

*Blood and the lymphatic system disorders:* anemia

*Immune system disorders:* allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)

*Psychiatric disorders:* anxiety

*Cardiac disorders:* tachycardia (including racing pulse, heart palpitations, heart pounding)

*Vascular disorders:* syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness

*Respiratory, thoracic and mediastinal disorders:* shortness of breath

*Gastrointestinal disorders:* dyspepsia

*Musculoskeletal, connective tissue and bone disorders:* back pain, leg pain

*Reproductive system and breast disorders:* uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea

*General disorders and administration site conditions:* pain

## 7 DRUG INTERACTIONS

### 7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

regimen is unknown. Refer to the follow-up assessment [see *Dosage and Administration (2.3)*] to verify that treatment has been successful.

### **7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)**

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

### **7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)**

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant patients are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant patients with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

#### Data

##### *Animal Data*

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

### **8.2 Lactation**

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with



misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

#### 8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

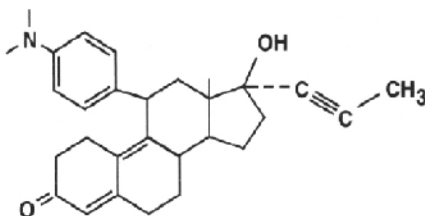
## 10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, the patient should be observed closely for signs of adrenal failure.

## 11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogesterational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11 $\beta$ -[p-(Dimethylamino)phenyl]-17 $\beta$ -hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is C<sub>29</sub>H<sub>35</sub>NO<sub>2</sub>. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The anti-progesterational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity

of prostaglandins.

## 12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotrophic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

## 12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for C<sub>max</sub> after single oral doses of 200 mg and 600 mg in healthy subjects.

### Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in females of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of  $1.98 \pm 1.0$  mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean C<sub>max</sub> was  $1.77 \pm 0.7$  mg/L occurring approximately 45 minutes after ingestion. Mean AUC<sub>0-∞</sub> was  $25.8 \pm 6.2$  mg\*hr/L.

### Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and  $\alpha_1$ -acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

### Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

### Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11β; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

### Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

### Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

#### Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

#### Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

## **14 CLINICAL STUDIES**

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.



**Table 3**  
**Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal)**  
**Through 70 Days Gestation**

	U.S. Trials	Non-U.S. Trials
<b>N</b>	16,794	18,425
<b>Complete Medical Abortion</b>	97.4%	96.2%
<b>Surgical Intervention*</b>	2.6%	3.8%
<b>Ongoing Pregnancy**</b>	0.7%	0.9%
<p>* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.</p> <p>** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.</p>		

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

**Table 4**  
**Outcome by Gestational Age Following Treatment with Mifepristone and**  
**Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies**

	≤49 days			50-56 days			57-63 days			64-70 days		
	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies
<b>Complete medical abortion</b>	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
<b>Surgical intervention for ongoing pregnancy</b>	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

is only available through a restricted program called the Mifepristone REMS Program [see *Warnings and Precautions* (5.3)].

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from [www.earlyoptionpill.com](http://www.earlyoptionpill.com).

### Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [see *Warnings and Precautions* (5.2)].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [see *Warnings and Precautions* (5.1, 5.2)].
- MIFEPREX is only available through a restricted program called the Mifepristone REMS Program [see *Warnings and Precautions* (5.3)]. Under the mifepristone REMS Program:
  - Patients must sign a Patient Agreement Form.
  - MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.

### Provider Contacts and Actions in Case of Complications

- Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, or if the patient experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever [see *Boxed Warning*].
- 

### Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to 14 days after taking MIFEPREX [see *Dosage and Administration* (2.3)].
- Explain that
  - prolonged heavy vaginal bleeding is not proof of a complete abortion,
  - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
  - it is recommended that ongoing pregnancy be managed by surgical termination [see *Dosage and Administration* (2.3)]. Advise the patient whether you will provide such care or will refer them to another provider.

### Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before resuming sexual intercourse.

MIFEPREX is a registered trademark of Danco Laboratories, LLC.

Manufactured for:  
*Danco Laboratories, LLC*  
P.O. Box 4816  
New York, NY 10185  
1-877-4 Early Option (1-877-432-7596)  
[www.earlyoptionpill.com](http://www.earlyoptionpill.com)

01/2023



<b>MEDICATION GUIDE</b>
<b>Mifeprex (MIF-eh-prex) (mifepristone tablets, for oral use)</b>
Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.
<b>What is the most important information I should know about Mifeprex?</b> <b>What symptoms should I be concerned with?</b> Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.
<b>Be sure to contact your healthcare provider promptly if you have any of the following:</b> <ul style="list-style-type: none"><li>• <b>Heavy Bleeding.</b> Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&amp;C).</li><li>• <b>Abdominal Pain or "Feeling Sick."</b> If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).</li><li>• <b>Fever.</b> In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.</li></ul>
<b>If you cannot reach your healthcare provider, go to the nearest hospital emergency room.</b>
<b>What to do if you are still pregnant after Mifeprex with misoprostol treatment.</b> If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.
<b>Talk with your healthcare provider.</b> Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.

**What is Mifeprex?**

**Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy.** Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

**Who should not take Mifeprex?**

Some patients should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

**What should I tell my healthcare provider before taking Mifeprex?**

**Before you take Mifeprex, tell your healthcare provider if you:**

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.  
Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

**How should I take Mifeprex?**

- Mifeprex will be given to you by a healthcare provider or pharmacy.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

**Follow the instruction below on how to take Mifeprex and misoprostol:**

**Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally**

**Day 1:**

- Take 1 Mifeprex tablet by mouth.

**24 to 48 hours after taking Mifeprex:**

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.



**Figure A** (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

**Follow-up Assessment at Day 7 to 14:**

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.



**When should I begin birth control?**

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

**What should I avoid while taking Mifeprex and misoprostol?**

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

**What are the possible side effects of Mifeprex and misoprostol?**

**Mifeprex may cause serious side effects. See "What is the most important information I should know about Mifeprex?"**

**Cramping and bleeding.** Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See "How should I take Mifeprex?" for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to 16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects. These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of Mifeprex.**

**Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.**

**For more information about Mifeprex, go to [www.earlyoptionpill.com](http://www.earlyoptionpill.com) or call 1-877-4 Early Option (1-877-432-7596).**

Manufactured for: *Danco Laboratories, LLC*  
P.O. Box 4816  
New York, NY 10185  
1-877-4 Early Option (1-877-432-7596) [www.earlyoptionpill.com](http://www.earlyoptionpill.com)

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 01/2023

MEMORANDUM

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

TO: FILE

FROM: [REDACTED] (b) (6) [REDACTED] (b) (6) Digitally signed by [REDACTED] (b) (6)  
Date: 2022.12.23 13:11:43 -05'00'

DATE: December 23, 2022

SUBJECT: Review of Supplemental Drug Applications Proposing Modifications to the Mifepristone REMS Program

FDA is currently reviewing a supplemental new drug application from Danco Laboratories, LLC (Danco) and a supplemental abbreviated new drug application from GenBioPro, Inc. (GBP) that propose to modify the Mifepristone Risk Evaluation and Mitigation Strategy (REMS) Program as approved under Danco's new drug application for Mifeprex (mifepristone) (NDA 020867) and GBP's abbreviated new drug application for Mifepristone Tablets 200 mg (ANDA 091178). Citing the Comstock Act, 18 U.S.C. §§ 1461, 1462, Plaintiffs in *Alliance for Hippocratic Medicine v. U.S. Food and Drug Administration*, No. 2:22-cv-00223-Z (N.D. Tex.), have alleged that FDA's actions regarding mifepristone do not comply with "federal laws that expressly prohibit the mailing or delivery by any letter carrier, express company, or other common carrier of any substance or drug intended for producing abortion" and also that FDA "failed to acknowledge and address" those laws. Complaint ¶¶ 22, 392 (Nov. 18, 2022). This memorandum notes that the Office of Legal Counsel of the United States Department of Justice, which provides controlling advice to Executive Branch officials on questions of law, has concluded that the Comstock Act provisions cited by Plaintiffs "[do] not prohibit the mailing of mifepristone or misoprostol where the sender lacks the intent that the recipient will use them unlawfully. And in light of the many lawful uses of mifepristone and misoprostol, the fact that these drugs are being mailed to a jurisdiction that significantly restricts abortion is not a sufficient basis for concluding that the mailing violates [these provisions]." Memorandum for Thomas J. Marshall, General Counsel, United States Postal Service, from Christopher H. Schroeder, Assistant Attorney General, Office of Legal Counsel, *Re: Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortions*, at 15 (December 23, 2022).<sup>1</sup> Thus, even if the Comstock Act provisions bear on FDA's analysis of the pending supplemental drug applications, in light of the conclusions set forth by the Office of Legal Counsel, they pose no issue for FDA's approval of the applications.

<sup>1</sup> The Office of Legal Counsel's analysis applies to 18 U.S.C. § 1461 and § 1462. See *id.* at 1 n.3.

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

**ALLIANCE FOR HIPPOCRATIC  
MEDICINE**, on behalf of itself, its member  
organizations, their members, and these  
members' patients, et al.,

Plaintiffs,

v.

**U.S. FOOD AND DRUG  
ADMINISTRATION**, et al.,

Defendants.

**Case No. 2:22-cv-00223-Z**

**DECLARATION OF DR. DONNA HARRISON**

I, Donna Harrison, a citizen of the United States of America and a resident of Berrien Center, Michigan, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified obstetrician and gynecologist.
3. I received my medical degree from the University of Michigan and completed my residency at a University of Michigan affiliate hospital, St. Joseph Mercy Hospital.
4. I am a diplomate of the American Board of Obstetrics and Gynecology.
5. I serve as the Chief Executive Officer of Plaintiff American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG).



6. I also serve as the Chair of the Board of Plaintiff Alliance for Hippocratic Medicine (AHM).
7. I am familiar with AAPLOG, its members, their fields of practice, and AAPLOG's policies and positions, including as set forth in the complaint, which I have reviewed.
8. AAPLOG is the largest organization of pro-life obstetricians and gynecologists ("OB/Gyns") in the world and is headquartered in Fort Wayne, Indiana. AAPLOG membership includes more than 6,000 medical professionals nationwide and more than 300 members in Texas. AAPLOG members practice in accordance with the Hippocratic oath, which forbids physician participation in killing their preborn patients in elective abortion. AAPLOG members are committed to the care and well-being of both of their patients including both pregnant women and the human beings in their womb. AAPLOG members are concerned about the serious adverse impacts of chemical abortion on both of their patients as well as on the practice of medicine.
9. I am also familiar with AHM, its members, their members' fields of practice, and AHM's policies and positions, including as set forth in the complaint, which I have reviewed.
10. AHM is a nonprofit organization that upholds and promotes the fundamental principles of Hippocratic medicine, which includes a prohibition on physician

involvement in killing their patients. AHM is incorporated in the State of Texas and has its registered agent in Amarillo, Texas.

11. AHM's members include the American Association of Pro-Life Obstetricians and Gynecologists, American College of Pediatricians, Catholic Medical Association, Christian Medical and Dental Associations, and Coptic Medical Association of North America. In opposing chemical abortion, AHM's members are concerned about the safety and well-being of pregnant women and girls, their preborn children, and chemical abortion's adverse impacts on the practice of medicine.
12. Through my work at AAPLOG and now AHM, I reviewed the studies on which the FDA has relied to make its 2016 Major Changes. The FDA identified these studies in its Summary Review document. App. 624–52.
13. The 2016 Summary Review “serves as the Division’s decisional memorandum.” *Id.* 628. The FDA noted that “[a]s these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes.” *Id.* 630.
14. As stated in Plaintiffs Complaint, App. 055–56, and Brief in Support of the Motion for Preliminary Injunction, p. 19, *none* of the studies on which the FDA relied were designed to evaluate the safety and effectiveness of chemical abortion drugs for use under the conditions prescribed, recommended, or suggested in the proposed labeling.

15. Not only did the FDA rely on studies that evaluated a drug regimen that did not match the labeling in the 2016 Major Changes, but the agency also took a piecemeal approach to evaluating the safety and effectiveness of its removal of necessary safeguards. App. 055–56. Safety must be evaluated under the totality of the proposed conditions of use, not each change in isolation of the other conditions. None of the cited studies actually mirrored the totality of changes in conditions of use allowed by the FDA 2016 Major Changes. Thus, none of the cited studies provides meaningful safety data to support the sweeping changes FDA made in 2016.

16. In Column A of the chart below, I have identified the studies that the FDA cited in its Summary Review. Column B identifies the major changes in the 2016 regimen for which FDA cited that study as support. Column C shows the conditions of use in the study that significantly differ from the conditions of use allowed in the approved 2016 label. Thus, Column C demonstrates why the particular cited study fails to show the safety of chemical abortion drugs for use under the conditions prescribed, recommended, or suggested in the proposed labeling of the 2016 Major Changes.



Study	FDA cited the study in support of the following Major Change(s)	Aspects of the study which significantly deviate from the conditions of use allowed by the 2016 Major Changes, rendering the citation invalid for showing safety under the 2016 label changes
<p>Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. <i>Obstet Gynecol</i> 2011;118:296-303.</p>	<ul style="list-style-type: none"> <li>• 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</li> <li>• Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex</li> <li>• Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex</li> </ul>	<ul style="list-style-type: none"> <li>• All patients had their gestational age confirmed by an ultrasound, which ruled out ectopic pregnancy and determined the exact gestational age.</li> <li>• All patients had witnessed ingestion of mifepristone but unknown time interval between mifepristone ingestion and misoprostol ingestion.</li> <li>• All patients had an in-person follow-up visit at 2 weeks after taking mifepristone, and an ultrasound was performed to ensure completion of the abortion.</li> <li>• The study was limited to 63 days' gestation or less.</li> </ul>

<p>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.</p>	<ul style="list-style-type: none"> <li>• 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</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective chart review study conducted in Australia.</li> <li>• All patients had gestational age and pregnancy location confirmed by ultrasound.</li> <li>• All patients had witnessed ingestion of mifepristone but unknown time interval between mifepristone ingestion and misoprostol ingestion.</li> <li>• 85% of patients who completed the study had in-person follow-up exam with ultrasound to confirm completion of abortion.</li> <li>• The study was limited to 63 days' gestation or less.</li> <li>• All women who were Rh negative received Rhogam.</li> <li>• Women at high risk of infection received prophylactic antibiotics.</li> </ul>
<p>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</p>	<ul style="list-style-type: none"> <li>• 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</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective study reviewed Medicaid diagnosis codes for complications treated in the ER after abortion, but study failed to provide the conditions to determine applicability to proposed labeling.</li> <li>• The study was limited 63 days' gestation or less.</li> </ul>

<p>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. <i>Obstet Gynecol</i> 2008;112(6):1303-1310.</p>	<ul style="list-style-type: none"> <li>• 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</li> <li>• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed</li> <li>• Increase the maximum gestational age from 49 days to 70 days</li> </ul>	<ul style="list-style-type: none"> <li>• Women required to be at least 18 years old.</li> <li>• Ultrasound performed to confirm gestational age of 57-70 days.</li> <li>• All patients had access to emergency transportation and a telephone.</li> <li>• Some patients were given antibiotics while others were not.</li> <li>• All patients had in person follow-up exam at the facility 7-14 days after mifepristone and had ultrasound to check for retained tissue.</li> </ul>
<p>Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. <i>Contraception</i> 2005; 72: 328-32</p>	<ul style="list-style-type: none"> <li>• 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</li> </ul>	<ul style="list-style-type: none"> <li>• All women had ultrasound to determine gestational age.</li> <li>• The study was limited to 56 days' gestation or less.</li> <li>• Women required to be at least 18 years old, or at least 16 years old with one parent's consent.</li> <li>• All women had observed ingestion of mifepristone in person.</li> <li>• All women who were Rh negative received Rhogam.</li> <li>• All women returned for an in-person follow-up exam before 15 days, which included an ultrasound to evaluation retained tissue.</li> </ul>



<p>Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. <i>Contraception</i> 2015; 91:269-273</p>	<ul style="list-style-type: none"> <li>• 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</li> <li>• 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</li> <li>• Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex</li> <li>• Increase in the maximum gestational age from 49 days to 70 days</li> </ul>	<ul style="list-style-type: none"> <li>• All patients had an ultrasound to determine gestational age.</li> <li>• All patients ingested mifepristone in the clinic.</li> <li>• All patients returned for in-person follow up visit at 10-14 days after taking mifepristone.</li> <li>• All patients received prophylactic antibiotics.</li> </ul>
<p>Raymond EG &amp; Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. <i>Obstet Gynecol</i> 2012; 119: 215-9</p>	<ul style="list-style-type: none"> <li>• 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</li> </ul>	<ul style="list-style-type: none"> <li>• This study has nothing whatsoever to do with misoprostol administration.</li> </ul>

<p>Raymond EG, et. al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. <i>Contraception</i> 2013; 87(1): 26-37.</p>	<ul style="list-style-type: none"> <li>• 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</li> <li>• Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex</li> <li>• Increase in the maximum gestational age from 49 days to 70 days</li> </ul>	<ul style="list-style-type: none"> <li>• This is not a clinical trial but rather a re-analysis of different studies under different non-comparable conditions at multiple locations around the world.</li> <li>• Of the 87 trials reviewed, only 19 were performed in the United States.</li> <li>• Of those 19 trials, 11 studied vaginal misoprostol exclusively. Of the remaining trials, only four studies analyzed buccal misoprostol. In one study the buccal misoprostol was administered simultaneously with mifepristone.</li> <li>• Gestational age determined by ultrasound or clinical examination.</li> <li>• Half of trial groups required ultrasound to assess failure.</li> <li>• The study limited to 63 days' gestation or less.</li> </ul>
<p>Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. <i>Obstet Gynecol</i> 2015;126:22-8.</p>	<ul style="list-style-type: none"> <li>• 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</li> <li>• Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex</li> </ul>	<ul style="list-style-type: none"> <li>• All patients had an ultrasound to determine gestational age.</li> <li>• Patients given mifepristone in the clinic at time of visit.</li> <li>• All patients had one week follow-up exam with ultrasonography.</li> <li>• The study limited to 63 days' gestation or less.</li> </ul>

<p>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.</p>	<ul style="list-style-type: none"> <li>• Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex</li> </ul>	<ul style="list-style-type: none"> <li>• This is not a clinical trial but rather a review of other studies. Five studies were reviewed. None of the 5 studies looked at buccal misoprostol.</li> <li>• Studies included in-person follow-up office visit with ultrasound after taking drugs.</li> </ul>
<p>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</p>	<ul style="list-style-type: none"> <li>• Administration of misoprostol at 24-48 hours instead of 48 hours after mifepristone</li> <li>• Addition that an 800 mcg buccal dose of misoprostol may be used if needed.</li> </ul>	<ul style="list-style-type: none"> <li>• This study examined vaginal administration of misoprostol, not buccal administration.</li> <li>• All women had an ultrasound to determine gestational age.</li> <li>• All women had in-person evaluations to rule out contraindications including labs for anemia and Rh type.</li> <li>• All women who were Rh negative received Rhogam.</li> <li>• Patients returned for two in-person follow-up visits (7 days and 14 days) where an ultrasound was performed at each visit.</li> </ul>



<p>Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. <i>Obstet Gynecol</i> 2013;121(6):1335-1347</p>	<ul style="list-style-type: none"> <li>Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex</li> </ul>	<ul style="list-style-type: none"> <li>This is not a clinical trial but rather a review of other studies.</li> <li>All of the studies reviewed used mifepristone and misoprostol for gestational ages between 12 and 20 weeks.</li> <li>Most studies in this review were not conducted in United States.</li> <li>Studies included buccal, vaginal, and oral routes of administration.</li> </ul>
<p>Phelps RH, et al. Mifepristone abortion in minors. <i>Contraception</i> 2001;64:339-343.</p>	<ul style="list-style-type: none"> <li>Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex</li> </ul>	<ul style="list-style-type: none"> <li>Pilot study included only 28 girls (ages 14-17 years old).</li> <li>Study examined vaginal, not buccal, administration of misoprostol.</li> <li>All girls had an in-person examination including ultrasound to determine gestational age.</li> <li>The study was limited to 56 days or less gestation.</li> <li>All were checked for anemia and Rh type.</li> <li>If Rh- then patient received Rhogam.</li> <li>Almost 1/3 of the girls had in-person administration of vaginal misoprostol with a 4-hour observation period after.</li> <li>Girls needed to live within 1 hour of research site.</li> </ul>

<p>Niinimaki M, et. al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. <i>BJM</i> 2011; 342: d2111.</p>	<ul style="list-style-type: none"> <li>Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex</li> </ul>	<ul style="list-style-type: none"> <li>Data from Finnish national database for abortions in Finland.</li> </ul>
<p>Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. <i>Obstet Gynecol</i> 2014;123:88-95.</p>	<ul style="list-style-type: none"> <li>Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex</li> </ul>	<ul style="list-style-type: none"> <li>Study conducted in Vietnam.</li> <li>Patients screened at in-person first visit.</li> <li>The study was limited to 63 days' gestation or less.</li> <li>Standard care compared with phone follow up only. Standard care entailed 2-week follow up in person with exam and ultrasound. Women with phone follow-up had to complete a semiquantitative urine pregnancy test and if the urine hCG dropped by one interval, the abortion was considered "a success."</li> </ul>
<p>Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? <i>Contraception</i> 2015;91:6-11.</p>	<ul style="list-style-type: none"> <li>Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex</li> </ul>	<ul style="list-style-type: none"> <li>Gestational age determined by ultrasound</li> <li>Data collected from Scotland.</li> <li>The regimen used vaginal, not buccal, administration.</li> </ul>

<p>Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. <i>Obstet Gynecol</i> 2012; 120: 1070-6</p>	<ul style="list-style-type: none"> <li>• Increase in the maximum gestational age from 49 days to 70 days</li> <li>• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed</li> </ul>	<ul style="list-style-type: none"> <li>• Gestational age confirmed by ultrasound.</li> <li>• Women were at least 18 years old.</li> <li>• Study required in-person follow-up visit with ultrasound.</li> <li>• Providers intervened surgically if necessary or at woman's request.</li> </ul>
<p>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. <i>Eur J Contracept Reprod Health Care</i> 2011; 16: 61-6</p>	<ul style="list-style-type: none"> <li>• Increase in the maximum gestational age from 49 days to 70 days</li> <li>• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed</li> </ul>	<ul style="list-style-type: none"> <li>• Gestational age confirmed by ultrasound.</li> <li>• Study conducted in Curacao.</li> </ul>
<p>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. <i>Reprod Health Matters</i> 2015; 22: 75-82</p>	<ul style="list-style-type: none"> <li>• Increase in the maximum gestational age from 49 days to 70 days</li> </ul>	<ul style="list-style-type: none"> <li>• Study performed in Mexico.</li> <li>• Women had initial in person visit where they swallowed mifepristone in the clinic.</li> </ul>



<p>Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousieiguez 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</p>	<ul style="list-style-type: none"> <li>• Increase in the maximum gestational age from 49 days to 70 days</li> </ul>	<ul style="list-style-type: none"> <li>• Study performed in Mexico.</li> <li>• All participants received in-person examination and ultrasound at first visit to determine gestational age and rule out ectopic pregnancy and other contraindications.</li> <li>• All participants had an in-person follow-up visit at 7-14 days with ultrasound to confirm complete passage of tissue.</li> </ul>
<p>Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015; 126(1): 12-21</p>	<ul style="list-style-type: none"> <li>• Increase in the maximum gestational age from 49 days to 70 days</li> </ul>	<ul style="list-style-type: none"> <li>• This is not a clinical trial but rather a review of published studies, including many of which are independently reviewed in this spreadsheet.</li> <li>• The study was limited to 63 days' gestation or less.</li> </ul>

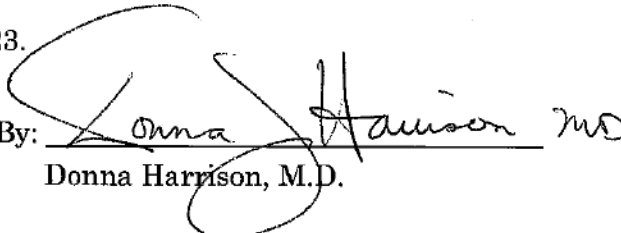
<p>Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. Eur J Contracept Reprod Health Care 2014; 19(6): 457-464</p>	<ul style="list-style-type: none"><li>• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed</li></ul>	<ul style="list-style-type: none"><li>• The study was performed in Azerbaijan.</li><li>• The study included only women 63 days' gestation or less.</li><li>• Participants had gestational age evaluated by history, exam, or ultrasound, but no data was included on what percent had these determinations.</li><li>• Study included women ages 18 or older.</li><li>• Women swallowed mifepristone in person in the clinic and then either took misoprostol buccally immediately in the clinic, or took later at home. Later study changed to sending women home with mifepristone and misoprostol.</li><li>• Two-week in-person follow-up exam at which time some women were evaluated with ultrasound (unknown %).</li></ul>
--	---	---

<p>Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. <i>Contraception</i> 2012; 86: 251-256</p>	<ul style="list-style-type: none"> <li>• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed</li> </ul>	<ul style="list-style-type: none"> <li>• The study was conducted in the Republic of Georgia and in Vietnam.</li> <li>• The study included only women 63 days' gestation or less.</li> <li>• Ultrasound was required at in-person visit.</li> <li>• Contraindications excluded from study.</li> <li>• Women swallowed the mifepristone at the clinic. Then randomized to 400 buccal misoprostol or 800 buccal misoprostol to be taken at home.</li> <li>• Women had in-person follow-up visit at two weeks.</li> </ul>
<p>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? <i>BJOG</i> 2007;114:271-278.</p>	<ul style="list-style-type: none"> <li>• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed</li> </ul>	<ul style="list-style-type: none"> <li>• The study was performed in India.</li> <li>• The study had an inclusion criteria "8 weeks of amenorrhea."</li> <li>• Gestational aged determined by clinical exam, LMP, and at times ultrasound (used as needed to determine age and ectopic pregnancy).</li> <li>• Misoprostol dose was not comparable to U.S. regimen: women were given 400 mcg of oral misoprostol, not buccal. Then the oral dose was repeated.</li> <li>• Women were observed up to 6 hours in the clinic.</li> <li>• Required in-person visit in 2 weeks with ultrasound for some.</li> </ul>



<p>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. <i>Contraception</i> 2006;74:36-41.</p>	<ul style="list-style-type: none"> <li>• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed</li> </ul>	<ul style="list-style-type: none"> <li>• This is not a clinical trial but rather a review of three studies, which investigated repeat misoprostol doses.</li> <li>• None of those studies looked at buccal administration of misoprostol.</li> </ul>
<p>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. <i>Lancet</i> 2011; 377: 1155-61</p>	<ul style="list-style-type: none"> <li>• Change of “physician” to “healthcare provider” in the label and Risk Evaluation and Mitigation Strategies (REMS) document</li> </ul>	<ul style="list-style-type: none"> <li>• The study was conducted in Nepal.</li> <li>• The study was limited to 63 days’ gestation or less and age confirmed by pelvic exam and LMP.</li> <li>• In-person vaginal administration three days later of misoprostol by the assigned abortion provider. After misoprostol placement, the woman was observed in the hospital for 3 hours.</li> <li>• Women had an in-person return visit in 10-14 days.</li> </ul>
<p>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. <i>Human Reprod</i> 2010;25(5):1153-1157.</p>	<ul style="list-style-type: none"> <li>• Change of “physician” to “healthcare provider” in the label and Risk Evaluation and Mitigation Strategies (REMS) document</li> </ul>	<ul style="list-style-type: none"> <li>• The study was conducted in Sweden.</li> <li>• Gestational age confirmed by ultrasound and exam.</li> <li>• Mifepristone administered in the hospital under direct observation.</li> <li>• Women self-administered vaginal misoprostol at home.</li> <li>• Women had an in-person follow-up exam after 2 weeks.</li> <li>• The study was limited to gestational ages between 50-63 days.</li> </ul>

Executed this February 24, 2023.

By:   
 Donna Harrison, M.D.