ACLU of Hawai'i Foundation

MATEO CABALLERO 10081
JONGWOOK "WOOKIE" KIM 11020
P.O. Box 3410
Honolulu, HI 96801
Telephone: (808) 522-5908
Facsimile: (808) 522-5909
E-mail: mcaballero@acluhawaii.org
wkim@acluhawaii.org

American Civil Liberties Union Foundation

JULIA KAYE*
SUSAN TALCOTT CAMP*
ANJALI DALAL*
RACHEL REEVES*
125 Broad Street, 18th Floor
New York, NY 10004
Telephone: (212) 549-2633
Facsimile: (212) 549-2650
E-mails: jkaye@aclu.org
tcamp@aclu.org
adalal@aclu.org
rreeves@aclu.org

*admitted *pro hac vice*

Attorneys for Plaintiffs

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAII

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

Plaintiffs,

vs.

ALEX M. AZAR, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]

PLAINTIFFS' CONCISE STATEMENT OF FACTS IN OPPOSITION TO DEFENDANTS' MOTION FOR SUMMARY JUDGMENT; CERTIFICATE OF SERVICE

Hearing: March 6, 2020, 9:00 a.m.
Judge: Hon. Jill A. Otake
Trial Date: Vacated per Dkt. 82
Related Document: Dkt. 89

Pursuant to Local Rule 56.1(e), Plaintiffs, by and through counsel, hereby submit their Opposition to Defendants' Concise Statement of Material Facts in Support of Defendants' Cross-Motion for Summary Judgment (Dkt. 90).

Plaintiffs' Responses to Defendants' Facts

1.	The Mifeprex REMS remained unchallenged until Plaintiffs initiated their lawsuit.	Compl. (D.E. 1)

Admitted.

2.	Mifepristone interrupts early pregnancy by blocking the effect of progesterone.	Compl. ¶ 54; *e.g.*, Supp. 20 Medical Review, Defs.' Ex. 22 at 0542; Questions & Answers on Mifeprex, Defs.' Ex. 31 at 0852.

Admitted. Mifepristone has additional effects that also contribute to the process of safely emptying the uterus. Decl. of Courtney Schreiber, M.D., M.P.H., attached as Ex. A to Pls.' Concise Statement of Facts Supp. Mot. for Summ. J. (Dkt. 87-1) ("Schreiber Support Decl."), ¶¶14-16.

3.	Misoprostol, when taken a day or two after Mifeprex, causes uterine contractions that expel the pregnancy from the uterus.	*See id.*

Admitted.

4.	Within a few days of taking Mifeprex and then misoprostol, the patient should experience a miscarriage.	*See id.*; Compl. ¶¶ 1, 57

Admitted.

5.	Pregnancy falls within the scope of subpart H because pregnancy can be serious for certain populations or under certain circumstances.	Citizen Petition Denial from FDA, Defs.' Ex. 32 at 0858-60

Admitted in part and denied in part.

Admitted that pregnancy can be serious for certain populations or under certain circumstances. Denied that pregnancy or medications relating to pregnancy "fall[] within the scope of Subpart H" because that is a legal conclusion, not a statement of fact.

6.	Medical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion.	Summary Review Memo, Defs.' Ex. 12 at 0228; *see also* 2000 REMS approval package and documentation, Defs.' Exs. 1-12

Admitted.

7.	In accordance with 21 C.F.R. part 314, subpart H, 21 C.F.R. 314.520, in its initial Mifeprex approval in 2000, FDA restricted the distribution of Mifeprex as specified in the approval letter.	Letter from CDER re: Approval (Sept. 28, 2000), Defs.' Ex. 2

Admitted that the FDA restricted distribution of Mifeprex as specified in the 2000 new drug application approval letter under 21 C.F.R. part 314, subpart H, 21 C.F.R. 314.520.

8.	The sponsor of the Mifeprex application and FDA agreed that approval under subpart H was appropriate.	Summary Review Memo (Sept. 28, 2000), Defs.' Ex. 12 at 0223, 0228

Admitted in part and denied in part.

Admitted that the FDA believed approval under subpart H was appropriate. Denied that the sponsor of the drug application believed approval under subpart H was appropriate. *Additional Excerpts from Administrative Record*, attached hereto as Ex. B ("Opp'n Ex. B"), at 0001-02 ("[W]e firmly believe that the NDA for mifepristone should *not* be approved under Sec. 314.520 [i.e., subpart H].") (emphasis added).

9.	FDA noted, "[l]abeling 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."	Summary Review Memo (Sept. 28, 2000), Defs.' Ex. 12 at 0224

Admitted that the FDA made this notation in 2000. Plaintiffs' admission does not address the truth of the statement or whether it was made in good faith.

10.	FDA also noted: "this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications."	Summary Review Memo (Sept. 28, 2000), Defs.' Ex. FDA 12 at 0228

Admitted that the FDA made this notation in 2000. Plaintiffs' admission does not address the truth of the statement or whether it was made in good faith.

11.	The Mifeprex Subpart H restrictions included a requirement that Mifeprex be provided by or under the supervision of a physician who can accurately assess the duration of a pregnancy, diagnose an ectopic pregnancy (for which Mifeprex is contraindicated), and provide—or otherwise assure access to—surgical intervention in cases of incomplete abortion or severe bleeding.	Letter from CDER re: Approval (Sept. 28, 2000), Defs.' Ex. 2 at 004; Summary Review Memo (Sept. 28, 2000), Defs.' Ex. 12 at 0228

Admitted.

12.	The original Mifeprex restrictions required Mifeprex to be dispensed to patients only in a clinic, medical office, or hospital, by or under the supervision of such physicians directly, and for the patient to take it in the physician's office.	Approved Labeling Text (Sept. 28, 2000), Defs.' Ex. 3 at 0016

Admitted in part and denied in part.

Admitted that the FDA's original restrictions on Mifeprex under Subpart H required that the drug be *dispensed* to patients only in a clinic, medical office, or hospital, by or under the supervision of such physicians. Denied that the FDA's original restrictions on Mifeprex under Subpart H required the patient to *take* the medication in the physician's office. Until 2016, the Mifeprex labeling (the FDA's only citation for this fact) specified that patients would take the Mifeprex "at [their] provider's office." However, it is undisputed that while restrictions under Subpart H or a REMS are mandatory, drug labeling is not: evidence-based "off-label" use of drugs is common and widely accepted. Schreiber Support Decl. ¶80; *see also, e.g.*, Pls.' Concise Statement of Facts Support Pls.' Mot. Summ. J. (Dkt.

87-11) ("PCSF") Ex. K, at 0295 (noting that although the "approved dosing [for Mifeprex] is 600 mg," "[s]tandard practice is to dispense a single, 200 mg tablet of mifepristone, not 600 mg"); Opp'n Ex. B, at 0594 (noting example of off-label use of Mifeprex by Planned Parenthood "since 2005"); *id.* at 0465 (describing request to "revise labeling in a manner that would reflect current clinical practice"); Joint Stipulation of Facts (Dkt. 85) ("Stips."), at ¶53 (2013 admission that taking Mifeprex under supervision "is not a REMS program requirement"); Stips. Ex. B, at 0258-260 (2011 REMS nowhere requiring that Mifeprex be taken onsite); Stips. ¶24 (2011 REMS contained "same requirements initially imposed in 2000").

13.	The Mifeprex safeguards initially imposed in 2000 have remained in place, largely unchanged, since that time.	2000 restrictions: *see* Letter from CDER re: Approval (Sept. 28, 2000), Defs.' Ex. 12; 2016 restrictions: *see* March 2016 Mifeprex REMS, JSF Ex. C; REMS Modification Review, JSF Ex. I at 0679-0680; Overview of 2016 REMS: *see* Defs.' Exs. 30, 31

Admitted in part and denied in part.

Admitted that the Mifeprex restrictions initially imposed in 2000 have remained in place, largely unchanged, since that time. Denied that these restrictions operate as "safeguards." *See* Pls.' Mem. of Law Opp'n Defs.' Mot. Summ. J. ("Pls.' Opp'n") 3–11.

14.	FDA approved the REMS in 2011 after evaluating the proposed REMS documents and REMS supporting document and concluding that they were acceptable.	Final Deemed REMS Review, Defs.' Ex. 13 at 0231-36; 2011 REMS, JSF Ex. B

Admitted.

15.	FDA reviewed the REMS in 2012, and again in 2015.	Review of Year 1 REMS (Aug. 2012) Defs.' Ex. 17; Review of Year 4 Rems (Oct. 2015) Defs.' Ex. 18

Admitted that the FDA reviewed the Mifeprex REMS in 2012 and 2015. In addition, in October 2012, the FDA's "Center [for Drug Evaluation and Research] Director requested that the REMS for Mifeprex be re-evaluated to determine if a REMS continues to be necessary," and in 2013, the Agency complied. Stips. Ex. H, at 0345.

16.	When evaluating the modifications to the REMS that Danco proposed in its 2016 sNDA, FDA fully considered whether each element of the REMS remained necessary to ensure the benefits outweighed the risks associated with Mifeprex.	2016 sNDA Approval Package, Defs.' Exs. 19-28; JSF Exs. A, C

Admitted in part and denied in part.

Admitted that the FDA evaluated each element of the Mifeprex REMS in 2015-2016 before determining that the REMS should be retained with only minor modifications. Denied that the FDA "fully considered" whether each element "remained necessary" as the FDCA requires. *See* Pls.' Opp'n 11–14.

17.	FDA's 2016 REMS evaluation included a multidisciplinary, multi-layered review.	2016 sNDA Approval Package, Defs.' Exs. 19-28; JSF Exs. A, C

Admitted.

18.	The 2016 review memoranda in the record include: a Summary Review, Cross Discipline Team Leader Review, Clinical Review, Chemistry Reviews, Pharmacology Review, Statistical Review, Clinical Pharmacology and Biopharmaceutics Reviews, Risk Assessment and Risk Mitigation Reviews, including a REMS Modification Review, other reviews including Labeling, and other internal memoranda and correspondence with the sponsor.	2016 sNDA Approval Package, Defs.' Exs. 20-28; JSF Exs. A, C, I

Admitted that the administrative record contains each of the above memoranda and other materials relating to the FDA's evaluation of the Mifeprex labeling and REMS in 2015-2016. However, the only 2016 document that "set[s] out the FDA's rationale for maintaining the Mifeprex REMS" is the 2016 *Risk Assessment and Risk Mitigation Review(s)* for Mifeprex ("2016 REMS Review"). Stips. ¶50 & Ex. I.

19.	The current Mifepristone REMS Program requires 1) Healthcare providers who prescribe mifepristone be specially certified. To become specially certified, healthcare providers must review the product labeling and complete a Prescriber Agreement Form. By signing a Prescriber Agreement Form, prescribers agree that they:	*See* March 2016 Mifeprex REMS, JSF Ex. C at 0404-0407; April 2019 Mifepristone shared REMS, Defs.' Ex. 33

	a) Have the ability to assess the duration of a pregnancy accurately, diagnose an ectopic pregnancy, provide a surgical intervention in cases of incomplete abortion or severe bleeding (or have made plans to provide such care through others), and assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and b) Will follow the guidelines for the use of mifepristone. The guidelines include reviewing the Patient Agreement Form and obtaining the patient's signature on the form, answering any questions the patient may have, signing the Patient Agreement Form, providing the patient with a copy of the Patient Agreement Form and the Medication Guide, recording in the patient's record the serial number of each mifepristone package dispensed, and reporting any deaths to the company that provided the mifepristone. 2) Dispensing of mifepristone only in certain health care settings. The sponsors must ensure that mifepristone will only be available to be dispensed in a clinic, medical office, or hospital, by or under the supervision of a certified prescriber. The sponsor must also ensure that mifepristone is not distributed to or dispensed through retail pharmacies or other settings not described above. 3) Dispensing of mifepristone only to patients with evidence or other documentation of safe use conditions. The patient must sign the Patient Agreement Form indicating that she has received, read, and been provided a copy of the Patient Agreement Form, as well as	

	received counseling from the prescriber regarding the risk of serious complications associated with mifepristone. 4) An Implementation System by which the sponsors ensure that mifepristone is only distributed to clinics, medical offices and hospitals by or under the supervision of a certified prescriber. The sponsors must ensure that mifepristone distributors comply with the program requirements for distributors, which include agreeing to ship the drug product only to clinics, medical offices, and hospitals identified by certified prescribers in their signed Prescriber Agreement Forms; and maintaining secure and confidential records of shipments. 5) REMS assessments must be conducted and submitted to FDA one year after the date of the approval of the REMS and every three years thereafter.	

Admitted.

20.	"[FDA] believes that the current safety profile [of Mifeprex] is reflective of an effective system in place with knowledgeable prescribers primarily using Mifeprex within that system guided by standard protocols. It is not likely that the current safe use conditions will persist to a similar extent if a REMS is no longer required and, as a consequence, we would expect a negative impact on the types, incidence, and severity of adverse events if the REMS was eliminated."	October 2013 Final REMS Review, JSF Ex. H at 0354

Admitted that the FDA stated this belief in 2013. Plaintiffs' admission does not address the truth of the statement or whether it was made in good faith.

21.	The 2016 approved sNDA and REMS changed the process for follow-up after administration of the Mifeprex regimen.	2011 Final deemed REMS Review, Defs.' Ex. 13 at 0241-42; Supp 20 Summary Review, Defs.' Ex. 20 at 0414, 0428

Admitted in part and denied in part.

Admitted that in 2016, the FDA changed the language relating to follow-up care in the Mifeprex *labeling and prescriber and patient agreement forms*. Denied that the Mifeprex REMS ever required a certain process for follow-up after administration of the Mifeprex regimen—beyond mirroring the description in the non-mandatory labeling. *See* Opp'n Ex. B, at 0594 ("It is important to note that since 2005, Planned Parenthood … 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."); *supra* Response to Defs.' ¶12.

22.	The 2016 REMS review involved the collaboration of many CDER offices and individuals in them.	2016 sNDA Approval Package, Defs.' Exs. 19-28; JSF Exs. A, C

Admitted.

23.	FDA ultimately concluded, "[b]ased on the available data and information, [FDA] continues to believe that a REMS is necessary to ensure the benefits outweigh the risks."	REMS Modification Review, JSF Ex. I, at 0702

Admitted that the FDA stated this conclusion in 2016. Plaintiffs' admission does not address the truth of the statement or whether it was made in good faith.

24.	The only Element to Assure Safe Use ("ETASU") that the 2016 REMS review teams recommended be removed from the REMS that was not removed was the Patient Agreement Form.	Supp. 20 summary review, Defs.' Ex. 20 at 0437-38; Supp. 20 Medical Review, Defs.' Ex. 22 at 0614-16; REMS Modification Review, JSF Ex. I at 0704-08

Admitted.

25.	In the years since approval with restrictions, millions of women in the United States have used Mifeprex with very few serious adverse events.	JSF ¶¶ 21, 57; Supp 20 Medical Review, Defs.' Ex. 22 at 0574- 76; Compl. ¶¶ 1, 3; Adverse Events Summary through 12/31/17, Defs.' Ex. 29

Admitted.

26.	Danco and GenBioPro, the sponsor of the generic version of Mifeprex, participate in a single, shared Mifepristone REMS Program.	Defs.' Ex. 33

Admitted.

27.	In its 2015 sNDA, Danco did not propose to eliminate or significantly modify the restricted distribution scheme for the drug.	Defs.' Ex. 20

Admitted.

28.	Danco requested that FDA approve: (1) an increase in the gestational age through which Mifeprex can be used from 49 days to 70 days; (2) a reduction in the Mifeprex dosage from 600-mg to 200-mg; (3) making an in-person patient follow-up visit with a healthcare provider a recommended advisement rather than a requirement; (4) elimination of the instruction that patients	Defs.' Ex. 20 at 0414-15

	take Mifeprex at their "provider's office"; (5) an expansion of the universe of healthcare providers who may prescribe Mifeprex to include all "healthcare providers," rather than just "physicians"; and (6) modifying the Medication Guide's risk-expectation advisement to note that "2-7 out of 100," rather than "5-8 out of 100," women "taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding."	

Admitted in part and denied in part.

Denied that Danco requested that the FDA modify the Medication Guide's risk-expectation advisement to say "2-7 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding"; the FDA's citation does not support this fact.

Otherwise, admitted, except to the extent it implies that Danco's requests to change the non-mandatory labeling (and any references thereto in the REMS documents) were requests to lift mandatory "requirement[s]." The change from 49 days to 70 days, the change in dosage from 600-mg to 200-mg, the changed reference to an in-person follow-up visit, elimination of the instruction that patients take Mifeprex at their "provider's office," and the reference to all "healthcare providers" rather than just "physicians" were all changes to the *labeling* (and references thereto in the REMS documents). Those labeling changes reflected evidence-based medical practice long pre-dating 2016. *See* Schreiber Support Decl.

¶80; PCSF Ex. K, at 0295 (noting that although the "approved dosing is 600 mg," "[s]tandard practice is to dispense a single, 200 mg tablet of mifepristone, not 600 mg"); Opp'n Ex. B, at 0594 (noting example of off-label use of Mifeprex by Planned Parenthood "since 2005"), 0465 (describing request to "revise labeling in a manner that would reflect current clinical practice").

29.	On April 11, 2019, FDA further maintained the REMS in approving an abbreviated new drug application for a generic version of Mifeprex.	ANDA Approval, Defs.' Ex. 34

Admitted.

30.	FDA determined that the Medication Guide helped "ensure dispensers provide important information to patients to enhance compliance with the regimen for safety and efficacy."	Defs.' Ex. 12 at 0224, 0226

Admitted that the FDA stated this determination in 2000 about the Medication Guide, which is still provided as part of the Mifeprex labeling but, as of 2016, is not a component of the Mifeprex REMS. *See supra* Response to Defs.' ¶19; Stips. Ex. I, at 0680, 0703 (discussing removal of Medication Guide as element of Mifeprex REMS but retention as part of the Mifeprex labeling). Plaintiffs' admission does not address the truth of the statement or whether it was made in good faith.

31.	FDA found the Patient Agreement to "foster[] active patient education and participation in this regimen."	Defs.' Ex. 12 at 0224

Admitted that the FDA made this statement in 2000. Plaintiffs' admission does not address the truth of the statement or whether it was made in good faith.

32.	By limiting distribution of Mifeprex to specified healthcare settings, FDA and the sponsor could ensure that patients were "properly counseled [at the time of dispensing Mifeprex] about the serious complications and what to do in the event that they experience an adverse event," which was considered vital to ensuring the safety of patients who use Mifeprex.	JSF Ex. H at 0346, 0356

Admitted in part and denied in part.

Admitted that the FDA made this statement in 2013. Denied that restricting where patients may obtain Mifeprex after it has been prescribed to them has any bearing on whether they will receive proper counseling. Further denied that the FDA in good faith "considered [this requirement] vital" to ensure proper counseling for Mifeprex without having identified any evidence that clinicians would not provide proper counseling and obtain informed consent for Mifeprex at the time of *prescription*, as numerous laws and ethical standards require and as they do for all other drugs. *See* Schreiber Support Decl. ¶¶58, 67; Pls.' Opp'n 4–6.

33.	The office constraints were consistent with the conditions of the clinical studies on which FDA's approval of the drug was based.	Defs.' Ex. 6 at 0035-0077; Defs.' Ex. 12 at 0223

Admitted to the extent that "office constraints" refers to the requirement imposed in 2000 pursuant to the FDA's Subpart H authority that Mifeprex be

dispensed only in designated health care settings (specifically, a clinic, hospital, or medical office) and not at a retail pharmacy.

34.	Mifeprex's sponsor proposed that patients have the option of taking the second drug in the regimen, misoprostol, on Day 3 of the regimen either at home (which is a departure from the conditions of use studied) or at the prescriber's office.	Defs.' Ex. 12 at 0224

Admitted that in 2000, the date of this citation, the Mifeprex sponsor proposed that the drug *labeling* reflect the option for patients to take the misoprostol at home. However, clinicians may deviate from a drug's labeling in accordance with evidence-based practice. *See supra* Response to Defs.' ¶12.

35.	FDA did not approve this option at the time because it found the data provided by the sponsor to support home use of misoprostol—which included "anecdotal off-label experience with a [different regimen], an observational study about home use in Guadeloupe, and a U.S. clinical study of home use of a different regimen"—did not provide substantial evidence for safety and efficacy.	Defs.' Ex. 12 at 0224

Admitted that in 2000, the date of this citation, the FDA did not approve the sponsor's proposed changes to the *labeling*, citing the lack of sufficient evidence of safety and efficacy to support home use of misoprostol. Plaintiffs' admission does not address the truth of the statement or whether it was made in good faith.

36.	FDA concluded that retaining the requirement that the drug be administered at the prescriber's office "assures that the misoprostol is correctly administered," and has the "additional advantage of contact between the patient and health care provider to provide ongoing care . . . ."	Defs.' Ex. 12 at 0225

Admitted in part and denied in part.

Admitted that the FDA stated these conclusions in 2000. Denied to the extent it implies that the language in the non-mandatory labeling (and any references thereto in the REMS documents) stating that patients take the misoprostol at their provider's office was ever a "requirement." *See supra* Response to Defs.' ¶¶12, 28. Plaintiffs' admission does not otherwise address the truth of the statement or whether it was made in good faith.

37.	Following the 2016 review, FDA approved each of the changes the sponsor proposed, with some modifications, concluding that the proposed changes were supported by appropriate data and information and consistent with the information submitted with the SNDA and FDA's finding that Mifeprex's "safety profile" had "not substantially changed."	Defs.' Ex. 20 at 0412-0439

Admitted.

38.	The approved labeling currently includes a black-box warning, which is required when there are certain contraindications or serious warnings, particularly those that may lead to death or serious injury, associated with the use of the drug product.	JSF Ex. A at 383-396; 21 C.F.R. § 201.57I(1)

Admitted. However, numerous drugs with black-box warnings, such as misoprostol, warfarin, and Korlym®, do not have a REMS. *See* Schreiber Support Decl. ¶¶36-37, 58; Opp'n Ex. B, at 0326; PCSF Ex. K, at 0300, 0305; Stips. ¶61.

39.	In conducting a REMS 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. The agency takes into consideration information from a variety of sources, including internal experts with specialized expertise relevant to the potential risks and, after products are approved, available post-approval information (such as adverse event reports and post-approval studies).	Defs.' Ex. 35 at 4-5

Admitted in part and denied in part.

Admitted that the FDA has published a guidance document stating that it considers the above factors and information in conducting a REMS analysis. Denied to the extent the FDA suggests that it considered all such factors and information *in evaluating the Mifeprex REMS* in 2016. *See generally* Stips. Ex. I; *see also* Pls.' Opp'n 11–14, 18–19.

40.	One statutory factor that helps determine if a REMS is needed is the "seriousness of any known or potential adverse events that may be related to the drug."	Defs.' Ex. 35 at 5-7

Admitted.

Plaintiffs' Additional Undisputed Material Facts in Opposition to Defendants' Motion for Summary Judgment

41.	Of the small number of patients who obtain additional clinical intervention after completing the mifepristone-misoprostol regimen, the vast majority do so for reasons other than a serious adverse event: (1) for ongoing pregnancy, (2) for incomplete abortion, or (3) at the patient's request.	Decl. of Courtney Schreiber, M.D., M.P.H., in Opp'n to Defs.' Mot. for Summ. J., attached hereto as Ex. A ("Schreiber Opp'n Decl."), at ¶¶3, 6; *see also* Stips. Ex. A, at 0390 (Table 2 in Mifeprex labeling listing "Serious Adverse Reactions Reported" following the mifepristone-misoprostol regimen, *not* including incomplete abortion or ongoing pregnancy), 0395 (Table 3 in Mifeprex labeling listing range of reasons for "surgical intervention"); Opp'n Ex. B, at 0435 (discussing "serious adverse events, ongoing pregnancy or incomplete abortion").
42.	An "incomplete abortion" means the regimen was not fully effective: although the pregnancy is no longer viable, tissue remains in the uterus.	Schreiber Opp'n Decl. ¶4.
43.	While a follow-up clinical intervention may be prudent in the case of an incomplete abortion or ongoing pregnancy to avoid the potential for a complication, incomplete abortion and ongoing pregnancy are not serious adverse events in and of themselves.	Schreiber Opp'n Decl. ¶4; Stips. Ex. A, at 0390; Opp'n Ex. B, at 0435.
44.	Cases of incomplete abortion can often be effectively treated with a repeat dose of misoprostol without the need for a follow-	Schreiber Opp'n Decl. ¶4; Opp'n Ex. B, at 0419–20; Stips. Ex. A, at 0386.

	up procedure to empty the uterus.	
45.	In virtually all of the few cases in which patients obtain a follow-up procedure after completing the mifepristone-misoprostol regimen, including in the extremely rare case of heavy bleeding, the "surgical intervention" is an extremely safe, five-minute vacuum aspiration procedure that does not involve any incisions, requires no anesthesia or sedation, and can be safely performed in a clinic or medical office.	Schreiber Opp'n Decl. ¶¶7–8.
46.	The statistic that "2-7 out of 100" Mifeprex users will obtain surgical intervention includes patients obtaining vacuum aspiration procedures at their own request rather than for any medical indication, typically to expedite completion of the abortion process.	Stips. Ex. A, at 0395 (Table 3); Schreiber Opp'n Decl. ¶5.
47.	Drug sponsors may have commercial reasons for wanting to maintain a REMS regardless of any medical need, such as to impede the entry of a generic drug into the market.	Statement from FDA Commissioner Scott Gottlieb, M.D., on new policies to reduce the ability of brand drug makers to use REMS programs as a way to block timely generic drug entry, helping promote competition and access (May 31, 2018), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-policies-reduce-ability-brand-drug-makers-use-rems.[1]

[1] Courts may take judicial notice of "government documents available from reliable sources on the Internet, such as websites run by governmental agencies." *Won v. Nelnet Servicing, LLC*, No. CV 18-00381 ACK-RLP, 2019 WL 1548572,

48.	The following statement appears in the black-box warning on the FDA-approved labeling for misoprostol: "PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS."	Cytotec® misoprostol tablets, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019268s051lbl.pdf (last visited Jan. 9, 2020).[2]
49.	The FDA concluded in 2012 that "it is unlikely that many pharmacies will keep Korlym stocked for the few patients eligible for treatment" but reasoned that "[d]istribution through a central pharmacy … ensures timely access to treatment."	Opp'n Ex. B, at 0328.
50.	One in four women in the United States will have an abortion in her lifetime.	Schreiber Support Decl. ¶8.
51.	The Secretary of Health and Human Services has delegated to the FDA all authority under the Food, Drug, and Cosmetic Act except where specifically statutorily prohibited.	FDA Staff Manual Guide 1410.10(1)(A)(1) (effective Aug. 26, 2016), https://www.fda.gov/media/81983/download (delegations of authority to the Commissioner of Food and Drugs).[3]

at *5 (D. Haw. Apr. 9, 2019); *accord Daniels-Hall v. Nat'l Educ. Ass'n*, 629 F.3d 992, 998-99 (9th Cir. 2010).

[2] *Id.*

[3] *Id.*

Dated: January 10, 2020.

Respectfully submitted,

/s/ Julia Kaye
JULIA KAYE*
SUSAN TALCOTT CAMP*
ANJALI DALAL*
RACHEL REEVES*
American Civil Liberties Union Foundation

/s/ Jongwook "Wookie" Kim
MATEO CABALLERO
JONGWOOK "WOOKIE" KIM
ACLU of Hawai'i Foundation

Attorneys for Plaintiffs

**Admitted Pro Hac Vice*

CERTIFICATE OF COMPLIANCE

I hereby certify that this document complies with the length limit of Local Rule 56.1(c) and the Court's order granting in part the parties' "Joint Motion for (1) Leave to Exceed the Page/Word Limits for Briefing on Cross-Motions for Summary Judgment; and (2) Summary Judgment Hearing on Proposed Dates and Continuance of Trial Date" (Dkt. 82) because, excluding the parts of the document exempted by Local Rule 7.4(d) and the language copied from Defendants' Concise Statement of Facts (Dkt. 90), it contains 2,327 words. In compliance with Local Rules 7.4(e) and 10.2(a), I further certify that this document has been prepared using Microsoft Word 2016 in 14-point Times New Roman font.

Dated: January 10, 2020.

/s/ Jongwook "Wookie" Kim
JONGWOOK "WOOKIE" KIM
ACLU of Hawai'i Foundation

Attorney for Plaintiffs

Exhibit A

Declaration of Courtney Schreiber, M.D., M.P.H., in Opposition to Defendants' Motion for Summary Judgment

ACLU of Hawai'i Foundation

MATEO CABALLERO 10081
JONGWOOK "WOOKIE" KIM 11020
P.O. Box 3410
Honolulu, HI 96801
Telephone: (808) 522-5908
Facsimile: (808) 522-5909
E-mails: mcaballero@acluhawaii.org
wkim@acluhawaii.org

American Civil Liberties Union Foundation

JULIA KAYE*
SUSAN TALCOTT CAMP*
ANJALI DALAL*
RACHEL REEVES*
125 Broad Street, 18th Floor
New York, NY 10004
Telephone: (212) 549-2633
Facsimile: (212) 549-2650
E-mails: jkaye@aclu.org
tcamp@aclu.org
adalal@aclu.org
rreeves@aclu.org

**admitted pro hac vice*

Attorneys for Plaintiffs

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAII

GRAHAM T. CHELIUS, M.D., *et al.*, Plaintiffs, vs. ALEX M. AZAR, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*, Defendants.	CIV. NO. 1:17-cv-00493-JAO-RT [CIVIL RIGHTS ACTION] **DECLARATION OF COURTNEY SCHREIBER, M.D., M.P.H., IN OPPOSITION TO DEFENDANTS' MOTION FOR SUMMARY JUDGMENT**

Courtney Schreiber, M.D., M.P.H., declares and states as follows:

1. This declaration in opposition to Defendants' motion for summary judgment incorporates the declaration I signed on November 13, 2019, in support of Plaintiffs' motion for summary judgment (Dkt. 87-1).

2. I understand that Defendants' motion refers to "Mifeprex's risks, which include incomplete abortion and serious bleeding that require surgical intervention in about 2-7 out of every 100 women who take the drug."

3. This statistic reflects the frequency with which patients have a follow-up procedure after using the mifepristone-misoprostol regimen—a procedure that, as I explain below, is exceedingly safe, simple, and common—due to any of several circumstances, most of which are not serious adverse events, much less medical emergencies. Of the small number of patients who obtain additional clinical intervention after the mifepristone-misoprostol regimen, the vast majority do so for reasons other than a serious complication: (1) ongoing pregnancy, (2) incomplete abortion, or (3) patient request.

4. "Ongoing pregnancy" means that the mifepristone-misoprostol regimen did not achieve the patient's desired outcome of ending the pregnancy. "Incomplete abortion" means that the regimen was not fully effective: the pregnancy is no longer viable, but there is some tissue retained in the patient's uterus. While under these circumstances follow-up clinical intervention may be

prudent to avoid the potential for a complication, ongoing pregnancy and incomplete abortion are not serious adverse events in and of themselves. Moreover, incomplete abortion does not necessarily require a *procedure* for treatment; this condition can often be resolved through an additional dose of misoprostol.

5. In addition, some patients who have used the mifepristone-misoprostol regimen may request a follow-up clinical procedure because they are uncomfortable with the bleeding that is an expected and safe outcome of medication abortion—i.e., the mechanism that empties the uterus—and wish to expedite completion of the abortion. The "2-7 out of 100" statistic includes such intervention at the patient's request.[1] This is simply a matter of patient preference, and is not medically indicated.

6. As the FDA has stated, serious adverse events relating to Mifeprex are "exceedingly rare, generally far below 0.1% for any individual adverse event."[2] In other words, among the few patients who obtain a follow-up procedure after completing the mifepristone-misoprostol regimen, only a tiny fraction do so

[1] Mifeprex Labeling 13 (Table 3), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[2] Ctr. For Drug Evaluation & Res., Application Number 020687Orig1s020: Medical Reviews 47 (Mar. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf.

because of a serious event, rather than the fairly routine (though infrequent) reasons of ongoing pregnancy, incomplete abortion, or patient request.

7. In all cases—both routine and, rarely, emergency—the follow-up "surgical intervention" is not what we typically think of as "surgery." In the first trimester of pregnancy, when all mifepristone-misoprostol abortions occur, the procedure used to evacuate the contents of a patient's uterus is known as vacuum aspiration (or "aspiration abortion"). While aspiration abortion is sometimes referred to as "surgical" abortion, this is a misnomer: the procedure involves no incisions into the patient's skin or other bodily membranes. Rather, the clinician inserts a small tube (or "cannula") through the cervix into the uterus. The tube is attached to a manual or electric pump, which evacuates the contents of the uterus with gentle suction. It is a minor procedure regularly performed on an outpatient basis that does not require anesthesia or sedation. The procedure takes about five minutes or less to complete and is one of the safest services in modern health care.[3]

8. In the rare circumstance that a person experiences heavy uterine bleeding—whether after the mifepristone-misoprostol regimen, after childbirth, or

[3] *See* Nat'l Acad. of Sci., Engineering, & Med., *The Safety and Quality of Abortion Care in the United States* 75 (2018), https://doi.org/10.17226/24950 (mortality risk for abortion is significantly lower than that of many other common medical procedures, such as colonoscopy and tonsillectomy); E. Hakim-Elahi et al., *Complications of First-Trimester Abortion: A Report of 170,000 Cases*, 76 Obstetrics & Gynecology 129 (Jul. 1990).

in a spontaneous abortion (i.e., miscarriage)—clinicians typically use this identical, safe aspiration procedure to treat the heavy bleeding. Accordingly, virtually all emergency departments have access to a physician who can perform this procedure, and the majority of clinicians who care for pregnant patients are trained in this procedure.

9. In addition, the "2-7 out of 100" statistic appears to reflect the outermost range, not the average, rate of "surgical intervention" following use of mifepristone and misoprostol. The Mifeprex labeling summarizes 22 worldwide clinical studies involving more than 35,000 patients, and states that 2.6% of patients in the U.S. studies and 3.8% of patients in the non-U.S. studies obtained clinical intervention following the mifepristone-misoprostol regimen.[4]

10. For all these reasons, the assertion that surgical intervention may be required for 2-7 out of every 100 patients who use the mifepristone-misoprostol regimen does not accurately reflect the extremely low risk that a patient using the mifepristone-misoprostol regimen will experience serious bleeding. It also fails to capture the nature of the minor, common, safe procedure used in the small fraction of cases when follow-up clinical care is appropriate.

[4] Mifeprex Labeling at 13 (Table 3).

I declare under penalty of perjury that the foregoing is true and correct.

Executed on January 2, 2020.

Courtney Schreiber, M.D., M.P.H.

Exhibit B

Additional Excerpts from Administrative Record in Opposition to Defendants' Motion for Summary Judgment

Exhibit B Index

Description	Date	Excerpted Bates Numbers
Mifeprex Sponsor Letter to FDA Center for Drug Evaluation and Research	January 21, 2000	0001-02
Korlym NDA Summary Review	February 17, 2012	0307, 0326, 0328
Mifeprex Supplemental NDA Summary Review	March 29, 2016	0412, 0419–20, 0435
Mifeprex Supplemental NDA Cross-Discipline Team Leader Review	March 29, 2016	0440, 0465
Mifeprex Supplemental NDA Medical Review	March 29, 2016	0527, 0594

The Danco Group

January 21, 2000

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-687, Mifepristone 200mg Oral Tablets**
- Amendment 039 - Mifeprex® – Distribution Plan

Dear D

As previously agreed, we are submitting Danco Laboratories, Inc.'s Distribution Plan for Mifeprex®. This is a comprehensive distribution plan that emphasizes control of mifepristone at all points in the supply chain, from manufacturers through to individual patients. This plan has been prepared in light of the unique situation surrounding abortion provision in the United States and not out of any medical safety concerns. However, in preparation of this plan, we have taken into account advice from the FDA that it is considering approving the NDA under "Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, Sec. 314.520--Approval with restrictions to assure safe use."

Our position is that we are willing to agree with the FDA on appropriate distribution controls for mifepristone but that the application of Sec. 314.520 under Subpart H seems unnecessary, in light of our voluntary acceptance of some appropriate distribution controls.

Specifically, Sec. 314.520(a) states that the FDA can apply post-marketing restrictions if it "concludes that a drug product shown to be effective can be safely used *only* if distribution or use is restricted" (emphasis added). Regardless of the distribution system for mifepristone, the medical safety of this drug is well documented in our IND application and in the label and, thus, we believe that Sec. 314.520 does not apply.

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is (

On the contrary, scientific evidence demonstrates that mifepristone is an exceptionally safe drug. Mifepristone when taken by a woman whose pregnancy is ≤ 49 days LMP is associated with several relatively minor and predictable side effects. 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. There has never been a death related to the use of mifepristone in combination with misoprostol for medical termination of pregnancy. These details have been discussed and reported in our label and various submissions to the FDA.

In addition to concerns about patient safety, the possibility of teratogenic effects has previously triggered the application of section 314.520, as in the case of Thalomid (Thalidomide). These concerns relate to the inadvertent use of a known teratogen at the early stages of a pregnancy that was not scheduled for termination. In contrast, all women who will receive mifepristone will be known to be in early pregnancy and have elected to terminate that pregnancy. Of course, in the case of a successful application of mifepristone, concerns about teratogenicity are rendered moot as the woman will no longer be pregnant. Similarly, in the case of a failed medical abortion, women should have a surgical intervention to terminate the pregnancy and are counseled to do so before taking mifepristone and misoprostol. To date, there is no compelling evidence to suggest that either mifepristone or misoprostol produces teratogenic effects.

Based on the above reasons, we firmly believe that the NDA for mifepristone should not be approved under Sec. 314.520. In addition, applying Sec. 314.520 might draw increased and unwarranted attention to the product, the FDA, and to Danco and its manufacturers, in particular evoking queries about the product's safety. Nonetheless, given the contentious political climate surrounding *all* abortion provision in the United States, we feel that the distribution of mifepristone should be carefully monitored and controlled. Therefore, we have developed and are implementing a controlled distribution strategy and are submitting the details of this strategy in the enclosed Distribution Plan for your review and comment.

Sincerely,

[redacted]

/[redacted]
Enclosure

cc: [redacted]
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
[redacted]

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s000

SUMMARY REVIEW

Prescriber labeling will include a BOXED WARNING

WARNING: TERMINATION OF PREGNANCY

See full prescribing information for complete boxed warning.

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

Under CONTRAINDICATIONS Section 4.1 the label will state:

4.1 Pregnancy

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

Under USE IN SPECIFIC POPULATIONS 8.1 Pregnancy:

8.1 Pregnancy

Category X

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

Under PATIENT COUNSELING INFORMATION

17.1 Importance of Preventing Pregnancy

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

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

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

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

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

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

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

- Recommendation for other Postmarketing Requirements and Commitments

The applicant will have two PMRs:

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

SUMMARY REVIEW

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

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

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

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

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

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

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

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

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

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

CROSS DISCIPLINE TEAM LEADER REVIEW

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

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

8.6.2 Advocacy Group Communications

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

MEDICAL REVIEW(S)

with a planned in-clinic follow-up. Women should be allowed to have an in-person visit if desired, but also allowed the flexibility of other options if desired.

It is important to note that since 2005, Planned Parenthood Federation of America has waived the follow-up visit if it poses undue hardships owing to distances from abortion facilities or other reasons, and women manage their follow-up with serial hCG testing.[74] From the clinical reviewers' perspective, this is safe and acceptable. We further note that the NAF 2015 guidelines (page 23) state the following:

> **"Success of the medical abortion must be assessed by ultrasonography, hCG testing, or by clinical means in the office or by telephone. If the patient has failed to follow-up as planned, clinic staff must document attempts to reach the patient. All attempts to contact the patient (phone calls and letters) must be documented in the patient's medical record."**

The ACOG 2014 Practice Bulletin[1] on management of early MAB states "Follow-up after receiving mifepristone and misoprostol for medical abortion is important, although an in-clinic evaluation is not always necessary." Several options for follow up without an office/clinic visit are discussed and no specific method or algorithm is definitely recommended (i.e., it is left to the discretion of the provider and patient).

Reviewer's Final Recommendation:

Based on the available evidence, flexibility in the timing and method of follow-up is safe to approve.

7.5 Supportive Safety Results

7.5.1 Common Adverse Events

According to the currently approved Mifeprex label,[75] common adverse events include the following:

- Vaginal bleeding up to 16 days, with 8% of women experiencing bleeding up to 30 days. 4.8% of women in the original US trials and 4.3% in the original French trials required administration of uterotonic agents to control the bleeding. Only 1% of women required intravenous fluids and 1% required curettage. In the original French trials, 5.5% of women had a drop in hemoglobin of more than 2 g/dL.
- Abdominal pain in 96% of US women
- Uterine cramping in 83% of French women
- Nausea in 43-61%, vomiting in 18-26%

[74] Fjerstad M. Figuring out follow-up. Mife Matters. Planned Parenthood Federation of America/Coalition of Abortion Providers 2006;13:2–3.

[75] http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.htm