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' MEMORANDUM OF LAW 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

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

I. INTRODUCTION

While the parties agree that the material facts in this case are undisputed, it is *Plaintiffs* who are entitled to judgment. The FDA's motion, like the administrative record on which it relies, lacks reasoned explanation, statutorily mandated analysis, or scientific evidence to support the Mifeprex REMS. These omissions are dispositive.

The Agency cannot explain why the Mifeprex REMS is "necessary to ensure that the benefits of [Mifeprex] outweigh the risks," 21 U.S.C. § 355-1(a)(1), or how the Prescriber Registration, Restricted Dispensing, or Patient Agreement ETASU mitigate Mifeprex's extremely rare risks. Instead, the FDA argues that the medical benefit "is self-evident," imploring the Court to blindly defer to the Agency's "scientific judgment" despite the absence of any supporting scientific evidence. Defs.' Mem. Law Supp. Mot. Summ. J. (Dkt. 91) ("Defs.' Mot.") 19-20. "The [Agency] cannot rely on reminders that its scientific determinations are entitled to deference in the absence of reasoned analysis to cogently explain" its action. *Nat. Res. Def. Council, Inc. v. Daley*, 209 F.3d 747, 755–56 (D.C. Cir. 2000).[1] The FDA's inability to articulate how the Mifeprex REMS enhances patient safety, much less point to any evidence supporting its theory, is fatal.

[1] Unless otherwise indicated, all internal marks and citations are omitted and all emphases are added.

Additionally, the FDA cannot identify where it satisfied the mandatory statutory criteria under the FDCA before imposing the Mifeprex REMS in 2016—because the administrative record is devoid of these required considerations. Where an agency "violate[s] Congress's precise instructions … that is the end of the matter." *Cook v. FDA*, 733 F.3d 1, 5, 10–11 (D.C. Cir. 2013) (striking FDA action that violated provision of FDCA which "unambiguously imposes mandatory duties"). For this reason, too, the Mifeprex REMS is invalid.

The FDA's arguments can neither cure nor distract from these critical omissions: highlighting updates to the drug treatment regimen that only underscore the illogic of the REMS; attempting to obscure Mifeprex's safety record with misleading references to its efficacy; speculating without evidence that Mifeprex's strong safety record is due to the REMS rather than the drug's inherent safety; and emphasizing its adoption of many of the drug sponsor's proposed modifications—as though that relieves the Agency of its statutory obligations.

These arguments are even less winning in a constitutional context. The FDA baldly asserts that the REMS imposes no undue burden and asks the Court to rubber-stamp that conclusion, ignoring that constitutional claims are reviewed *de novo*. *McNary v. Haitian Refugee Ctr., Inc.*, 498 U.S. 479, 493 (1991). Indeed, the FDA's motion only bolsters Plaintiffs' constitutional claims—admitting, for instance, that delaying access to medication abortion harms patients, Defs.' Mot.

20, 24-25, when it is undisputed that the Mifeprex REMS causes such delay, *see* Pls.' Concise Statement Supp. Mot. Summ. J. (Dkt. 87) ("PCSF") ¶65, among myriad other harms. With no plausible medical benefit to outweigh them, *all* of these undisputed burdens are undue. Moreover, because there is no rational explanation why clinicians seeking to prescribe Mifeprex face burdensome regulations from which clinicians prescribing similar or riskier drugs are immune, the REMS also violates equal protection as a matter of law.

II. ARGUMENT

A. The Mifeprex REMS Violates the APA

1. The FDA Offers No Reasoned Explanation, Much Less Evidence, Supporting the Mifeprex REMS

The FDA may impose a REMS only if "necessary to ensure that the benefits of the drug outweigh [its] risks." 21 U.S.C. § 355-1(a)(1). It may impose ETASU, which further restrict access, only when "required as part of [a] strategy to mitigate a specific serious risk listed in the labeling of the drug." *Id.* § 355-1(f)(1), (f)(1)(A). To meet these statutory requirements, the FDA cannot merely *assert* that the Mifeprex REMS enhances the drug's safety—it must *explain how* the REMS as a whole and each ETASU (Restricted Dispensing, Prescriber Registration, and Patient Agreement) actually "mitigate" the risk that a patient will experience "serious or fatal bleeding or infections," the two serious risks listed in the labeling. The FDA can survive arbitrary and capricious review only if, "after a searching

and careful inquiry" of the record, the Court believes the Agency has "articulate[d] a satisfactory explanation," supported by "substantial evidence in the administrative record," for reauthorizing the REMS and each ETASU in 2016. *See Nat'l Lifeline Ass'n v. FCC*, 921 F.3d 1102, 1111 (D.C. Cir. 2019). But the FDA did not, and cannot, do so.

There is no explanation or evidence underlying the Mifeprex REMS—neither in the 2016 REMS Review that was the exclusive basis for the challenged agency action, nor in the 2013 REMS Review on which the FDA principally relies in this motion. Instead, contrary to common sense and with no scientific support, the Agency speculates that, without the REMS, Mifeprex prescribers *might* engage in practices that would be unlawful, unsafe, and unethical—for *any* of the thousands of FDA-regulated drugs that are not subject to a REMS. Such baseless speculation cannot justify a REMS. *See Comcast Corp. v. FCC*, 579 F.3d 1, 7 (D.C. Cir. 2009) (agency's asserted justification for rule capping cable operators' market share percentage of subscribers "warrants little discussion" where based on "conjecture" with "no record support" and contradicted by "common knowledge").

a. Restricted Dispensing

The FDA argues that the Restricted Dispensing ETASU (1) ensures proper counseling and (2) prevents treatment delay. Defs.' Mot. 20. Both theories are illogical and belied by the undisputed evidence.

First, regarding counseling, the Agency argues in its entirety:

> [L]imiting distribution of the drug to specified healthcare settings 'contributes to the patient's safe use of Mifeprex by making the prescriber responsible for giving the drug directly to the patient and counseling the patient at the time of dispensing' …. Dispensing the drug in broader settings, such as through retail pharmacies, might expose patients to unnecessary and increased risks because they would not receive counseling about the serious complications associated with Mifeprex or what to do if experiencing an adverse event when they receive the drug.

Id.; *accord id.* at 14–15.

This is not how medicine works: For nearly all of the 20,000 drugs it regulates, the FDA trusts the *prescriber* to provide appropriate counseling and obtain informed consent, as numerous laws and professional standards require, regardless of where the patient fills the prescription. Joint Stipulation of Fact (Dkt. 85) ("Stips.") ¶58; PCSF ¶18. The FDA requires that only 15 drugs, including Mifeprex and its generic, be dispensed in designated healthcare settings and not at a pharmacy. Stips. ¶60. And of these 15, Mifeprex and its generic are the *singular exception*: for the remaining 13 drugs, there is an actual clinical reason—other than "counseling"—why the patient must receive and take the drug onsite: it must be either administered by a clinician (*e.g.*, intravenously) or monitored by a clinician during administration (*e.g.*, to respond to immediate life-threatening reactions). *See* Pls.' Mem. Law Supp. Summ. J. (Dkt. 86-1) ("Pls.' Mot.") 17.

The FDA provides no evidentiary support for its conjecture that, absent this restriction, abortion providers "might" not properly counsel patients at the time of prescription, as they do for all drugs. Just the opposite: the FDA's 2016 REMS Review admits that "comprehensive patient counseling and informed consent prior to medical or surgical abortion treatment is standard of care"—a practice that cannot be a function of the REMS, since there is no REMS for surgical abortion. Stips. ¶57. Moreover, the FDA trusts clinicians prescribing misoprostol, the second in the two-drug medication abortion regimen, to convey the black-box warning that "PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS," Pls.' Concise Statement Opp'n Defs.' Mot. Summ. J. ("PCSF Opp'n") ¶¶38, 48—misoprostol is available at a pharmacy. Stips ¶61. In short, the undisputed evidence contradicts this rationale.

Second, regarding delay, the Agency argues only: "[P]atients may delay picking up their Mifeprex prescription from the pharmacy, or may have difficulty finding a pharmacy that stocks the drug; initiating an abortion after such delay could result in increased complications." Defs.' Mot. 20; *accord id.* at 24. This rationale cannot be squared with the undisputed fact that the FDA allows patients to swallow the Mifeprex at home. Stips. ¶29. If avoiding delayed administration of the abortion regimen were a motivating factor for the Restricted Dispensing

ETASU, the FDA would not have removed the labeling instruction that patients take the Mifeprex "in [their] provider's office" in 2016, and would not trust patients to fill their misoprostol prescriptions at the pharmacy. *Id.* ¶61; PCSF ¶22.

The record does not support the FDA's speculation that patients "may" unsafely delay taking Mifeprex simply because they receive it in a pharmacy rather than a clinic. To the contrary, in updating the labeling, the FDA relied on a study finding "no significant difference in either efficacy or safety" for participants who took Mifeprex at home rather than in a clinic. PCSF ¶22. The FDA provided no evidence on pharmacy willingness to stock Mifeprex, nor considered the ubiquity of misoprostol (which is also an abortifacient). *See* PCSF ¶¶79, 83. Moreover, in its review of Korlym® (mifepristone for Cushing's syndrome), the FDA found it "unlikely that many pharmacies will keep Korlym stocked"— but reasoned that "[d]istribution through a central pharmacy" could "ensure[] timely access to treatment." PCSF Opp'n ¶49. Yet the Agency nowhere considered whether Mifeprex could be made available through a specialty pharmacy.

Because the FDA has "offered an explanation for its decision that runs counter to the evidence before the agency, [and] is so implausible that it could not be ascribed to a difference in view or the product of agency expertise," this ETASU is arbitrary and capricious. *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

b. Prescriber Registration

The FDA argues that (1) if not for this ETASU, "prescribers unfamiliar with Mifeprex could prescribe it, potentially increasing the risk of serious complications," Defs.' Mot. 23, and (2) this ETASU "ensure[s] that patients will have access to appropriate medical care in the event of a serious adverse event," *id.* at 20; *accord id.* at 13. Both rationales are entirely speculative, contradicted by FDA admissions, and equally applicable to countless other drugs without a REMS.

First, the FDA specifically asserts that this ETASU limits Mifeprex prescribers to clinicians who "are very familiar with managing early pregnancies," are "able to accurately date pregnancies," and will not prescribe Mifeprex when contraindicated or beyond the ten-week limit listed in the labeling. *Id.* at 13, 23. But *all* drugs carry risks, Stips. ¶2, and would be unsafe if prescribed by clinicians unfamiliar with the medication or its contraindications. For nearly all of the 20,000 prescription drugs the FDA regulates, it addresses those risks without a REMS, relying on the numerous laws and ethical standards prohibiting clinicians from prescribing medications outside their competency or outside the standard of care—the same laws and standards that prevent clinicians from prescribing blood thinners to patients with bleeding disorders, or prescribing misoprostol for ulcer treatment

to a pregnant patient. *See* Stips. ¶¶58–61; PCSF ¶¶18, 79, 86. The Agency presented no evidence that such laws and standards are inadequate for Mifeprex.[2]

Second, the Agency asserts that Prescriber Registration is necessary to ensure access to emergency care. Defs.' Mot. 13, 20. But the requirement that Mifeprex prescribers have a plan to ensure access to surgical care, transfusions, or resuscitation in the "exceedingly rare" event of a serious complication, PCSF ¶8, means only that the prescriber is able to direct the patient to the nearest emergency department—something every clinician can do, *id.* ¶19.

The FDA has not presented any "reasoned analysis to cogently explain" why the Prescriber Registration is necessary to ensure clinicians prescribe Mifeprex only when medically appropriate, or to ensure access to basic emergency care in the extremely rare event it is needed. *Daley*, 209 F.3d at 755–56. Accordingly, this ETASU is arbitrary and capricious.

c. Patient Agreement

The Patient Agreement is, likewise, a solution in search of a problem. To justify it, the FDA relies exclusively on the unsubstantiated assertion of a political appointee that the Patient Agreement "provide[s] additional assurance that the patient is aware of the nature of the procedure, its risks, and the need for

[2] Moreover, it is undisputed that the only skills the FDA deems essential for Mifeprex prescribers—dating and diagnosing an intrauterine (*i.e.*, non-ectopic) pregnancy—are possessed by virtually every clinician caring for pregnant patients, PCSF ¶21, and otherwise easily substituted by ordering an ultrasound, Stips. ¶67.

appropriate follow-up care." Defs.' Mot. 24; Stips. ¶41. But the Commissioner cited no evidence in overruling the FDA scientists' recommendation to eliminate this requirement, and the CDER Director cited no evidence in instructing her staff to comply. Stips. ¶41 & Ex. I, at 0674. By contrast, the record contains extensive, undisputed evidence that the Patient Agreement is "duplicative," "burden[some]," and "does *not* add to safe use conditions." Stips. ¶41; PCSF ¶25. The Agency's eleventh-hour, politically motivated action is the epitome of arbitrary and capricious. *See Tummino v. Torti*, 603 F. Supp. 2d 519, 544–45 (E.D.N.Y. 2009), *amended sub nom. Tummino v. Hamburg*, No. 05-CV-366 ERK VVP, 2013 WL 865851 (E.D.N.Y. Mar. 6, 2013) (agency action invalid if based even "in part on the pressures emanating from political actors" (quoting *D.C. Fed'n of Civic Assocs. v. Volpe,* 459 F.2d 1231, 1246, 1248 (D.C. Cir. 1971))).

d. Mifeprex REMS as a Whole

It is undisputed that: (1) the serious risks listed in the Mifeprex labeling are "exceedingly rare, generally far below 0.1% for any individual adverse event"; (2) "no causal relationship … has been established" between the use of Mifeprex/misoprostol and these adverse events; (3) the same risks of infection and bleeding exist any time the pregnant uterus is emptied, whether through childbirth, miscarriage, surgical abortion, or medication abortion; and (4) "the physiology of pregnancy may be a more plausible risk factor" than Mifeprex for any rare

infections following use. Stips. ¶19; PCSF ¶¶8–12; *see also* Pls.' Mot. 6–8. Unable to articulate, much less prove, that the Mifeprex REMS mitigates any of these rare risks inherent to *pregnancy*, the Agency asks the Court to accept its word, asserting that "[t]he effectiveness of the Mifeprex REMS in mitigating the drug's undeniably serious potential risks is self-evident." Defs.' Mot. 20.

While deference is indeed owed to expert scientific judgments, deference cannot insulate an action devoid of either science or expertise. *See infra* 16–20. Where the Agency "has failed to offer a reasoned explanation [for its action] that is supported by the record," *Am. Tel. & Tel. Co. v. FCC*, 974 F.2d 1351, 1354 (D.C. Cir. 1992), the action is arbitrary and capricious and must be "set aside," 5 U.S.C. § 706(2). As a matter of law, "[our reasoning] is self-evident" fails the APA, and it is *Plaintiffs* who are entitled to summary judgment.

2. <u>The FDA Did Not Consider the Mandatory Statutory Factors</u>

Congress unequivocally stated that the Agency may impose a REMS only where "*necessary* to ensure that the benefits of the drug outweigh the risks of the drug"; that the Agency "*shall* consider" six enumerated benefit/risk factors in making that determination; and that ETASU "*shall* … not be unduly burdensome on patient access to the drug, considering in particular … patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)." 21 U.S.C. §355-1(a)(1), (f)(2)(C), (f)(2)(C)(ii). "The case law provides

ample support" that "the ordinary meaning of 'shall' is 'must.'" *Cook*, 733 F.3d at 7 (discussing mandatory duties under the FDCA). Yet the 2016 REMS Reauthorization satisfied none of these unambiguous statutory commands.

First, the 2016 REMS Review nowhere explained why a REMS was necessary to ensure Mifeprex's benefits outweigh its rare risks. *See* Stips. Ex. I. The Agency's motion underscores this deficiency. Defs.' Mot. 16–21 (five-page section explaining 2016 action citing 2016 REMS Review only once); *accord id.* at 7–8 (quoting 2013 analysis to justify 2016 action, with only a "*see also*" citation to the 2016 REMS Review).

Even imagining, counter-factually, that the 2016 REMS Review had been informed by the 2013 analysis[3]—and that this earlier analysis actually contained evidence or reasoned analysis supporting the Mifeprex REMS, which it does not, *see supra* 3–11—the 2016 action would still violate the statutory mandate. Far from explaining why the REMS remained necessary, the 2016 FDA reviewers extensively documented why the Patient Agreement is *unnecessary* for patient safety, and offered only a conclusory assertion that the "benefit risk balance of Mifeprex [would] remain[] favorable" as long as the other two ETASU are retained. Stips. ¶57 & Ex. I, at 0680–81. Under the APA, agency decisions must be both "reasonable and reasonably explained," *Carlson v. Postal Regulatory*

[3] The 2013 REMS Review was *not* among the "[m]aterials informing" the 2016 REMS Review. PCSF ¶17.

Comm'n, 938 F.3d 337, 343–44 (D.C. Cir. 2019), and the "explanation may not be superficial or perfunctory," *Owner-Operator Indep. Drivers Ass'n, Inc. v. Fed. Motor Carrier Safety Admin.*, 656 F.3d 580, 588–89 (7th Cir. 2011) (where statute said regulation "shall ensure" vehicle monitoring devices not be used to harass vehicle operators, agency assertion that it "took the statutory requirement into account" was insufficient: agency needed to "reveal[] how it drew the line between legitimate measures … and forbidden measures that harass" and, relying on a study or something comparable, "describe what precisely it is that will prevent harassment from occurring"). The FDA did not provide the reasoned explanation the APA requires.

After finding in 2016 that the Patient Agreement was *unnecessary* in part because "[s]erious adverse events are rare and the safety profile of Mifeprex has not substantially changed," Stips. Ex. I, at 0681, the Agency now attempts to invert that conclusion, arguing that Mifeprex's consistently excellent safety record was its reason for maintaining the REMS, Defs.' Mot. 16, 20. The only 2016 document "set[ting] out the FDA's rationale for maintaining the Mifeprex REMS," Stips. ¶50, provides no support for that assertion—so the Agency cites without specificity to a different 2016 memorandum, Defs.' Mot. 16 (citing all 27 pages of Defs.' Ex. 20, Summary Review). The FDA violated the FDCA by failing to explain in 2016 why the Mifeprex REMS remained necessary.

Second, while the FDA asserts in the abstract that REMS decisions are "grounded on a thorough review of the underlying science and careful consideration of the regulatory and statutory requirements," it cannot identify where in 2016 it considered (much less "thorough[ly]" and "careful[ly]" reviewed) the mandatory statutory factors. Defs.' Mot. 11; PCSF ¶16. Tellingly, the FDA's discussion of the six benefit/risk factors and the "complex, drug-specific inquiry" it undertakes before imposing a REMS cites only to generic guidance documents—not to any such analysis for Mifeprex. Defs.'Mot. 17–18. "Even when an agency has significant discretion in deciding how much weight to accord each statutory factor," it is not "free to ignore any individual factor entirely." *Carlson*, 938 F.3d at 344. Here, the FDA ignored *every* factor, in violation of the APA.[4]

Third, the FDA flouted the FDCA's unambiguous requirement that ETASU "shall … not be unduly burdensome" on patients, particularly those "in rural and medically underserved areas." 21 U.S.C. §355-1(f)(2)(C), (f)(2)(C)(ii). For the Restricted Dispensing and Prescriber Registration ETASU, the Agency ignored

[4] The Korlym REMS Review illustrates the comprehensive inquiry that the FDCA requires and stands in stark contrast to the FDA's treatment of Mifeprex. It includes sections on, *inter alia*, "Size of Population," "Expected Drug Benefit," "Duration of Treatment," "Severity of Risk," "Risk in Context of Drugs in Class and among Other Drugs Used to Treat the Disease," and "How the Risk(s) are Managed across Other Products and/or Diseases." PCSF Ex. K, 0296-0301. It considered three "Risk Management Options"—two REMS or "No REMS and voluntary restricted distribution through specialty pharmacies/distributors"—before deciding upon the latter. *Id.* at 0302-0303. The Agency also identified "burden to the intended population" as an "important factor." *Id.* at 0301.

this statutory mandate altogether: not a single word in the 2016 REMS Review addresses whether and to what extent these ETASU burden access. For the Patient Agreement, the Agency relied only on the Commissioner's conclusory assertion that retaining this ETASU "would not interfere with access," Stips. Ex. I, at 0674—a statement unsupported by any evidence and contradicted by the scientific review team's finding that the Patient Agreement is "a burden for patients," PCSF ¶25. Indeed, there is undisputed evidence that the Patient Agreement undermines informed consent when it is inconsistent with a patient's clinical circumstances, and causes confusion and distress. *Id.* ¶¶28–29.

The FDA's disregard of this statutory requirement is all the more egregious because the Agency possessed evidence that the Mifeprex REMS particularly harms rural and low-income patients. *See* PCSF ¶61; Pls.' Mot. 12, 24–25. Its failure to consider a part of the ETASU analysis that Congress deemed essential is fatal.[5] *Owner-Operator*, 656 F.3d at 587 ("When Congress requires an agency to address something … that factor is by definition an 'important aspect of the problem' under *State Farm*"); *Nat'l Lifeline*, 921 F.3d at 1112–13 (APA violation where agency did not consider providers' unwillingness to offer services to low-

[5] Underscoring the importance of this concern, Congress also required the FDA to "seek input … about how [ETASU] … for 1 or more drugs may be standardized so as not to be … unduly burdensome on patient access," and to "periodically evaluate" the ETASU for 1 or more drugs to assess whether the elements … are not unduly burdensome on patient access," 21 U.S.C. §355-1 (f)(5).

income individuals as a result of agency action or impact on those consumers).

Because the FDA's imposition of the Mifeprex REMS in 2016 was "inconsistent with the statutory mandate" in multiple respects, it is the Court's "clear duty … to reject" it. *S.E.C. v. Sloan*, 436 U.S. 103, 118–19 (1978).

3. The FDA's Arguments Cannot Cure Its Deficient Analysis

To deflect attention from these analytical and statutory defects, the FDA makes five arguments: (a) General principles of deference excuse the lack of reasoned explanation for the Mifeprex REMS, *see* Defs.' Mot. 11–13; (b) the Court should consider Mifeprex's efficacy rate, *see id.* at 1, 14, rather than the FDA's admission that individual adverse events are "generally far below 0.1%," PCSF ¶8; (c) the Court should assume, absent any evidence, that the REMS is "likely" responsible for Mifeprex's excellent safety record, *see* Defs.' Mot. 19–20, 24–25; (d) the FDA's adoption of changes proposed by the drug sponsor relieve the Agency of its independent statutory obligations; and (e) Plaintiffs should be "[]satisfied" with the updates to the Mifeprex treatment regimen, including explicitly authorizing patients to swallow at home the medication they must receive in a medical office, *see id.* at 1–2, 7. Each is meritless.

a. Deference Cannot Rescue a Decision Grounded in Neither Reason Nor Evidence

The FDA argues that this Court should simply trust the Agency's "conclusion that the Mifeprex REMS remains necessary in light of the drug's

risks[, because this] is a quintessential scientific judgment that readily passes muster under the APA's deferential standard." Defs.' Mot. 11–13. But the APA standard is not "blind faith," *Comm. for an Indep. P-I v. Hearst Corp.*, 704 F.2d 476, 473 (9th Cir. 1983), and deference to a reasoned, evidence-based judgment does not mean rubber-stamping a groundless decision, *Daley*, 209 F.3d at 755–56 (agency "cannot rely on reminders that its scientific determinations are entitled to deference in the absence of reasoned analysis"). Courts regularly reverse actions implicating an agency's core expertise where they are ill-reasoned,[6] inconsistent with other agency actions,[7] not based on the relevant factors,[8] or ignore significant evidence.[9] *See State Farm*, 463 U.S. at 43.

The 2016 REMS Reauthorization suffers from each of these deficiencies. The FDA (1) offered no reasoning at all for plainly illogical restrictions, *supra* 3–

[6] *E.g.*, *Nat'l Parks Conservation Ass'n v. EPA*, 788 F.3d 1134, 1141–43 (9th Cir. 2015) (rejecting regulation requiring power plants to implement certain emission-reducing technologies where agency did not explain why it selected those technologies or how it determined cost-effectiveness).

[7] *E.g.*, *Calif. v. U.S. Dep't of Health & Human Servs.*, 941 F.3d 410, 430 (9th Cir. 2019) (blocking implementation of rules creating religious and moral exemptions to Affordable Care Act's contraceptive coverage mandate).

[8] *E.g.*, *Mich. v. EPA*, 135 S. Ct. 2699, 2706 (2015) (rejecting regulation of air pollutants where agency did not consider compliance costs).

[9] *E.g.*, *Tenneco Gas v. FERC*, 969 F.2d 1187, 1214 (D.C. Cir. 1992) (failure to consider relevant evidence in the record "falls afoul of [the] requirement that an agency engage in reasoned decisionmaking by supporting its conclusions with 'substantial evidence' in the record").

11, (2) treated Mifeprex inconsistently with other, riskier drugs, Pls.' Mot. 14–18; (3) failed to consider the mandatory statutory factors, *supra* 11–16; and (4) ignored evidence from medical experts that the REMS provides no medical benefit while burdening access, Pls.' Mot. 11–12. Deferring to such a defective decision would be "tantamount to abdicating the judiciary's responsibility under the [APA]." *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1491 (D.C. Cir. 1995) (rejecting FDA's finding that drug was biological equivalent of similar drugs approved for sale).

Moreover, Courts do not accord deference to abstract technical expertise that the Agency nowhere exercised. *Turlock Irrigation Dist. v. Fed. Energy Reg. Commn.*, 903 F.3d 862, 873 (9th Cir. 2018) ("In the absence of evidence that [an agency]'s interpretation was 'clearly based' on its technical expertise, we do not defer."). The FDA asserts that its REMS decisions warrant deference because they are based on a "complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors." Defs.' Mot. 17. But it cites only to generic guidance documents—instructions for how its expertise *should* be employed in a REMS determination—without referencing a single piece of scientific evidence supporting the Mifeprex REMS, much less a logical connection between such evidence and the restrictions. *Id.* at 17, 19 (citing Defs.' Ex. 35, FDA's general guidance for the industry). It is not enough for the FDA to baldly assert that, "based on its expertise and experience," the Agency "would expect a negative

impact on the types, incidence, and severity of adverse events if the REMS was eliminated." Defs.' Mot. 18. The FDA must show its work, not merely tell the Court to trust its word. *See Carlson*, 938 F.3d at 344 (agency decision must be "reasonably explained"); *Comcast Corp.*, 579 F.3d at 7 (dismissing agency "conjecture" with "no record support").

The Commissioner's interference with the Mifeprex REMS determination underscores why deference is inappropriate. Citing no evidence, the Commissioner overruled the scientific review team's only major REMS decision grounded in research: that the Patient Agreement "does not add to safe use conditions" and "burden[s]" patients. Stips. ¶41; PCSF ¶25, 32; Pls.' Mot. 13–14, 37–39. Not only does this extraordinary political intervention evidence bad faith—making the REMS decision *per se* arbitrary and capricious, *see* Pls.' Mot. 37–39—it also demonstrates that the 2016 REMS Reauthorization did *not* "implicate[] FDA's undisputed technical expertise," Defs.' Mot. 13.

In short, the FDA's motion cites no evidence that the 2016 action rested on technical expertise, while Plaintiffs cite undisputed evidence that it was tainted by political considerations. Deference cannot salvage this decision. *See, e.g.*, *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 185, 192 (E.D.N.Y. 2013) (striking restrictions on emergency contraception because the "action was politically motivated, scientifically unjustified, and contrary to agency precedent").

b. The FDA Tries to Obscure Mifeprex's Strong Safety Record with Misleading References to Its Efficacy

The Agency asserts that the REMS is "necessary given 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." Defs.' Mot. 1; *accord id.* at 14 ("serious risks" include "bleeding and incomplete abortion" which can "require patients to independently seek emergency surgical intervention"). These statements are at best irrelevant and at worst misleading.

First, the FDA's statistic suggests that 2-7% of Mifeprex users experience serious bleeding. *See* Defs.' Mot. 1. This profoundly misconstrues Mifeprex's risks: the Agency admits that the rate of serious complications is "generally far below 0.1% for any individual adverse event." PCSF ¶8. Instead, the vast majority of patients captured by the FDA's 2-7% statistic obtain a follow-up intervention for one of three reasons—(1) ongoing pregnancy; (2) incomplete abortion, or (3) at the patient's request—*none* of which the FDA identifies as "serious adverse reactions." PCSF Opp'n ¶¶43, 46. For instance, where the patient requests a follow-up procedure to expedite completion of the abortion, that is simply a matter of personal preference, not a medical indication. *Id.* ¶46.

Second, the FDA's statistic intimates that any intervention following the Mifeprex regimen is necessarily an "emergency surgical intervention." Defs.' Mot. 14. This is false. In the three scenarios above, and generally even in the (very rare)

case of heavy bleeding, the follow-up procedure is an extremely safe, five-minute, vacuum aspiration procedure that can be performed in-office without anesthesia or sedation. PCSF Opp'n ¶45. And it is undisputed that in cases of incomplete abortion, even this minor procedure is not "require[d]," *see* Defs.' Mot. 1—as the Mifeprex labeling explains, a repeat dose of misoprostol is often sufficient to complete the abortion, Stips. Ex. A, at 0386; PCSF Opp'n ¶44.

c. The FDA Cannot Use a Drug's Inherent Safety to Justify a Permanent REMS

The FDA speculates that Mifeprex's strong safety record is "likely reflective" of its restricted access. Defs.' Mot. 25; *accord id.* at 19–20. It makes this assertion with neither evidence nor any plausible explanation of how the Mifeprex REMS actually enhances patient safety (for instance, how a patient's location when she is handed a pill she will swallow at home has any bearing on the likelihood of infection or bleeding). *See supra* 3–11.

As a matter of law, such baseless conjecture is insufficient under the APA. *Comcast Corp.*, 579 F.3d at 7. Moreover, if such speculation were sufficient to justify a REMS, the FDA could never be held accountable for missteps: it could always credit a strong safety record to the REMS rather than the drug's inherent safety. This cannot be squared with Congress's clear intent to ensure that REMS programs do not needlessly restrict drug access. *See* Pls.' Mot. 5–6 (detailing statutory limitations).

Even assuming *arguendo* that the Mifeprex restrictions were warranted when originally imposed in 2000 because they "were similar to conditions of the U.S. clinical trial for the drug," Defs.' Mot. 5, "the [Mifeprex REMS] imposes current burdens and must be justified by current needs," *Shelby Cty., Ala. v. Holder*, 570 U.S. 529, 536 (2013). The FDA violated the APA when it renewed the REMS in 2016 with neither discussion nor evidence that these restrictions remained necessary to ensure Mifeprex's benefits outweigh its rare risks.

d. The FDA's Statutory Obligations Do Not Turn on the Drug Sponsor's Requests

The FDA repeatedly emphasizes that it adopted most of Danco's proposed REMS modifications, as though this justifies the Agency's decision. *See, e.g.*, Defs.' Mot. 1–2, 7. This is irrelevant as both a legal and a practical matter.

The government, not the drug sponsor, is the subject of the statutory constraints on REMS programs, *e.g.*, 21 U.S.C. §355-1(a)(1), (f)(1), and drug sponsors may have commercial reasons for wanting to maintain a REMS regardless of any medical need (such as to impede entry of a generic), PCSF Opp'n ¶47. Thus the FDA may initiate a REMS review on its own initiative, 21 U.S.C.§ 355-1(g)(4)(B),[10] as the Agency did here. In 2015–2016, the FDA "considered whether *each* element of the REMS remained necessary," Defs.' Mot. 16; Stips.

[10] Consistent with the FDCA, the Secretary delegates REMS decisions to the FDA, 21 U.S.C.§ 355-1(a)(4); PCSF Opp'n ¶51.

¶37—not just those modifications that Danco had proposed, Pls.' Opp'n ¶28. The evidence established that the Mifeprex REMS did not meet the statutory criteria, and thus the Agency had an independent duty to eliminate it.

e. The FDA's 2016 Updates to the Mifeprex Labeling Make Its Retention of the REMS Even Less Reasonable

Finally, the FDA suggests that Plaintiffs should be "[]satisfied" with the updates to the Mifeprex treatment regimen, such as eliminating the labeling instruction that patients take the medication in [their] "provider's office."[11] Defs.' Mot. 1–2. Far from proving the FDA's reasonableness, the Agency's removal of the labeling statement that a patient takes the Mifeprex at her provider's office only underscores the illogic of demanding that she receive it there. By specifically indicating that patients can take the Mifeprex at home, the FDA concedes that there is no need for clinicians to either administer or supervise the administration of Mifeprex, in contrast to *all* the other 13 drugs with restricted dispensing requirements. *See supra* 5.

[11] The FDA inaccurately describes its updates to the Mifeprex *labeling* as having "eased restrictions" under the *REMS*. Defs.' Mot. 1–2, 5. While the **labeling** (from which clinicians are free to deviate in accordance with the standard of care, PCSF ¶¶26–27) previously stated that patients take the Mifeprex "in [their] provider's office," the **REMS** (which is *mandatory regardless* of the standard of care) never required patients to swallow the medication onsite, *id.* ¶53 (2013 admission that taking Mifeprex under supervision "is not a REMS program requirement"). Regardless, this distinction is immaterial: it is undisputed that, as of 2016, neither the REMS nor the labeling states that patients swallow the pill onsite. *Id.* ¶29.

B. The Mifeprex REMS Violates the Constitution

1. The Mifeprex REMS Poses an Undue Burden

The undue burden test requires balancing "the burdens a law imposes on abortion access together with the benefits th[e] law[] confer[s]." *Whole Woman's Health v. Hellerstedt*, 136 S. Ct. 2292, 2309 (2016), *as revised* (June 27, 2016); *accord Planned Parenthood Ariz., Inc. v. Humble*, 753 F.3d 905, 914 (9th Cir. 2014). The Mifeprex REMS cannot survive such balancing. On one side of the scale, there is undisputed evidence that these restrictions block and delay abortions and pose an array of other harms. PCSF ¶¶36–68. On the other, there is the utter lack of evidence supporting the purported benefits, *see supra* 3–11, and the explicit finding of the FDA's scientific review team that the Patient Agreement "does *not* add to safe use conditions," PCSF ¶25. The FDA's request for blind deference can no more protect the Mifeprex REMS in the constitutional context than it could as a statutory matter—indeed, far less, given *de novo* constitutional review. Because the REMS imposes undisputed and unjustified burdens, it is unconstitutional. Because a large fraction of impacted patients suffer such burdens, facial relief is proper.

a. The FDA's Argument for Deference is Even Weaker in a Constitutional Challenge

Plaintiffs' constitutional claims require independent assessment of both the facts and the law. *Pickering v. Bd. of Educ. of Twp. High Sch. Dist. 205*, 391 U.S. 563, 569–70 n.2 (1968); *see also, e.g.*, *Chen-Li Sung v. Doyle*, 988 F. Supp. 2d

1195, 1204 (D. Haw. 2013), *aff'd sub nom. Sung v. Doyle*, 670 F. App'x 560 (9th Cir. 2016).[12] Nevertheless, the FDA argues that the Court should rubber-stamp the REMS instead of meaningfully applying the undue burden test because the Agency "unquestionably brings a wealth of knowledge and experience to bear in the realms of science and public health." Defs.' Mot. 27. But the Agency here cites *Hellerstedt*—a case that involved no agency action and only underscores that "*the 'Court retains an independent constitutional duty to review factual findings where constitutional rights are at stake*.'" 136 S. Ct. at 2310 (emphasis in original).[13]

Courts routinely block abortion restrictions that states defend as benefiting women's health, even where they bear the imprimatur of state health officers or the FDA. *See, e.g.*, *EMW Women's Surgical Ctr., P.S.C. v. Glisson*, No. 3:17-CV-00189-GNS, 2018 WL 6444391, at *27 (W.D. Ky. Sept. 28, 2019) (striking regulations requiring abortion clinics to have written transfer agreement with local

[12] Review is *de novo* as to both Plaintiffs' stand-alone constitutional claims and claims under 5 U.S.C. § 706(2)(B) ("contrary to constitutional right"). *See, e.g.*, *McNary*, 498 U.S. at 493; *Carpenter v. Mineta*, 432 F.3d 1029, 1032 (9th Cir. 2005); *All. for Nat. Health US v. Sebelius*, 786 F. Supp. 2d 1, 12 n.10 (D.D.C. 2011) (*de novo* review regardless of "whether the plaintiff sues directly under the Constitution or under the [APA]" (quoting *Rydeen v. Quigg*, 748 F. Supp. 900, 905 n.8 (D.D.C. 1990)).

[13] The FDA's citation to *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach* likewise does not support blind deference. *Abigail* considered not a well-established right such as abortion, but "whether there" even exists "a constitutional right to assume … 'enormous risks'" pursuing "drugs with no proven therapeutic effect." 495 F.3d 695, 710 (D.C. Cir. 2007).

hospital, finding "the record … devoid of any credible proof that the challenged regulations have any tangible benefit to women's health"); *W. Ala. Women's Ctr. v. Williamson*, 120 F. Supp. 3d 1296, 1317 (M.D. Ala. 2015) (plaintiffs likely to succeed in undue burden challenge to regulation requiring abortion providers to have hospital admitting privileges or contract with doctor with such privileges). Notably, in *Humble*, the Ninth Circuit invalidated a state law requiring adherence to the FDA's Mifeprex labeling, concluding that the law "appears wholly unnecessary as a matter of women's health." 753 F.3d at 915.

While courts may defer to "an agency's assessment of scientific or technical data within its area of expertise" even in a constitutional challenge, *Sebelius*, 786 F. Supp. 2d at 12, the FDA performed no such scientific or technical assessment here, *see supra* 18–19. Nor did the Agency consider the extent to which the Mifeprex REMS burdens patient access. *See supra* 14–16. Even if the Agency had weighed the asserted benefits of the Mifeprex REMS against its burdens (which it did not), its conclusion would be irrelevant to the Court's constitutional analysis: "courts, not agencies, are experts on constitutional issues." *Rydeen*, 748 F. Supp. at 906 (citing *Porter v. Califano*, 592 F. 2d 770, 780 n.15 (5th Cir. 1979)).

b. The Mifeprex REMS Imposes Undisputed Burdens with No Countervailing Interest

Where an abortion restriction is "sought to be justified on medical grounds," "[t]he feebler the medical grounds, the likelier the burden, even if slight, is to be

'undue.'" *Humble*, 753 F.3d at 914. Because the REMS is plainly illogical, *see supra* 3–11, even minimal burdens could not pass constitutional muster.

But this case presents a far more lopsided scale. Limiting where patients may obtain medication abortion is not merely "incidental" to the Mifeprex REMS, Defs.' Mot. 25 (citing *Planned Parenthood of Se. Penn. v. Casey*, 505 U.S. 833, 874 (1992))—it is precisely the point. And there is extensive, undisputed evidence that these restrictions interact with "women's lived experience, socioeconomic factors," and other "practical considerations," *Humble*, 753 F.3d at 915 (citing *Casey*, 505 U.S. at 887–94), to cause substantial harm.[14]

It is undisputed that delay increases the health risks associated with abortion, Defs.' Mot. 20, 24; *see also Humble*, 753 F.3d at 915–17, and indisputable that the REMS delays abortion access, PCSF ¶¶50, 61–68. It is undisputed that pregnancy and childbirth pose life-threatening risks far exceeding those of abortion, PCSF ¶11, and indisputable that the REMS forces women to carry unwanted pregnancies to term, PCSF ¶¶50, 61–64. It is also indisputable that the REMS, both by

[14] The FDA's suggestion that the Court ignore the realities of women's lives relies on two inapposite cases regarding the constitutionality of excluding abortion from government *benefit* programs—*i.e.*, whether there is an affirmative right to financial assistance for abortion. Defs.' Mot. 25–26 (citing *Rust v. Sullivan*, which held that indigent women are not entitled to abortion counseling or referrals in the federal Title X program, 500 U.S. 173, 201 (1991), and *Maher v. Roe*, which held that Medicaid may exclude abortion from coverage, 432 U.S. 464, 473–74 (1977)). *Humble*, which considered the constitutionality of *restrictions* on medication abortion, establishes the relevant legal standard.753 F.3d at 915.

involving more people in the abortion care process and by increasing travel, logistics, and time away from work for people seeking abortions, jeopardizes patients' ability to keep their abortion decisions confidential, compromising their privacy, safety, and economic stability. PCSF ¶¶43, 58–59; *see, e.g.*, *Planned Parenthood of Ind. & Ky. Inc. v. Comm'r of Ind. State Dep't of Health*, 896 F.3d 809, 819 (7th Cir. 2018) (considering "concerns about confidentiality in employment situations and abusive spouses" in blocking abortion restriction).[15]

Having nothing with which to dispute Plaintiffs' evidence of harm, the FDA offers a logical fallacy: "the REMS is not a substantial obstacle to women seeking a medical abortion—as demonstrated by the millions who have used the drug since 2000." Defs.' Mot. 27. This facile observation ignores the undisputed evidence that many more people *would have* used Mifeprex if not for the REMS: it is undisputed that one in four women in the United States will have an abortion in her lifetime, PCSF Opp'n ¶50, and that some who seek an abortion cannot obtain one, PCSF ¶¶62–64. Moreover, because the REMS causes delay and myriad other harms, it is

[15] It is of no moment that Plaintiffs omitted from their Complaint a citation "for the remarkable proposition that any regulation that has the effect of causing some doctors to provide referrals for a particular type of abortion creates an undue burden." Defs.' Mot. 26. Plaintiffs offer no such proposition; they challenge not "*any* regulation" that may prompt abortion referrals, only *this* regulation that forces qualified clinicians to turn away patients seeking medication abortions for no articulable reason. PCSF ¶¶36–47. Moreover, "case law citations and/or quotations … are entirely unnecessary" in a complaint. *Hunt v. Yoshimura*, No. 19-CV-00490-DKW-RT, 2019 WL 6499083, at *1 (D. Haw. Dec. 3, 2019).

an undue burden "even if some women … will nonetheless obtain an abortion." *Humble*, 753 F.3d at 917.

c. The Mifeprex REMS Poses an Undue Burden for a Large Fraction of Impacted Patients and Therefore Is Facially Invalid

An abortion restriction is facially invalid where the law is an undue burden for a "large fraction" of impacted patients. *Casey*, 505 U.S. at 895; *see also Isaacson v. Horne*, 716 F.3d 1213, 1230–31 (9th Cir. 2013) (explaining that whether an abortion restriction is unconstitutional "in all cases, or only in some cases to which it applies, may affect the breadth of the relief to which plaintiffs are entitled but not … the constitutional standard we apply," and thus the "large fraction" test is a question of remedy). That remedy test is easily met here.

The Supreme Court instructs courts applying the large fraction test to ignore "the group for whom the law is irrelevant"—here, patients whose providers *are* able to comply with the REMS—and focus only on the group for whom the law operates as a restriction. *Casey*, 505 U.S. at 895 (in challenge to spousal notification mandate, denominator of large fraction test was "married women seeking abortions who do not wish to notify their husbands … and who do not qualify" for an exemption). Accordingly, the proper focus of this Court's inquiry is people seeking medication abortions whose clinicians must turn them away because of the Mifeprex REMS. *All* such patients face burdens—at a minimum, all

are delayed in accessing time-sensitive care and must bear the risks and burdens of pregnancy longer, PCSF ¶¶65–68—and, lacking any countervailing medical benefit, *see supra* 3–11, *all* these burdens are undue. The large fraction test is readily exceeded; therefore, the proper remedy is facial relief.

2. The Mifeprex REMS Violates Equal Protection By Burdening Mifeprex Prescribers But Not Clinicians Prescribing Similar or Riskier Drugs

The FDA's motion nowhere addresses a simple classification: the Agency's disparate treatment of clinicians seeking to prescribe Mifeprex as compared to clinicians seeking to prescribe drugs with comparable or less favorable risk profiles, such as mifepristone for treatment of Cushing's syndrome (Korlym), misoprostol for use in a medication abortion, or anticoagulants. *See, e.g.*, Defs.' Mot. 28–33 (arguing that the REMS does not "disproportionately impact[] women, women seeking abortion, women with limited financial means, or drug products approved for medical abortion with assertedly similar risks as other non-abortion drug products"); Pls.' Mot. 15–17 (discussing risk profiles for Korlym, misoprostol, and anticoagulant warfarin). Plaintiffs do not need heightened scrutiny to prevail, *see* Defs.' Mot. 31, because the Agency does not—and cannot—explain why this disparate treatment is rational, *see id.* at 19. Its singular treatment of abortion providers defies common sense, and thus fails even rational basis review. *See* Pls.' Mot. 14–17, 41–42.

III. CONCLUSION

The undisputed facts show that *Plaintiffs*, not the FDA, are entitled to summary judgment. Plaintiffs respectfully move the Court for judgment as a matter of law.

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), it contains 7,493 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.

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]

52 pages have been withheld as b4 (CCI) immediately following this page

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:

---

[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