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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAIʻI

GRAHAM T. CHELIUS, M.D., *et al.*, Plaintiffs, v. ALEX M. AZAR, II, M.D., M.P.H., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*, Defendants.	CIV. NO. 1:17-00493 JAO-RT **DEFENDANTS' MEMORANDUM IN OPPOSITION TO PLAINTIFFS' CROSS-MOTION FOR SUMMARY JUDGMENT** Hearing scheduled for March 6, 2020, at 9am Judge Otake

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INTRODUCTION

Plaintiffs would have this Court believe that, in 2016, FDA "severely restricted access to a safe and effective drug for termination of early pregnancy." Pls.' Mem. in Support of Pls.' Mot. For Summ. J. at 1 (Dkt. No. 86-1) ("Pls.' MSJ"). In reality, FDA did nothing but maintain safeguards on the drug—Mifeprex—that have mitigated the drug's risks to patients since its initial approval in 2000. Those risks include serious infection and sometimes-life-threatening bleeding or incomplete abortion that requires surgical intervention in about 2-7 out of every 100 women who take the drug.

In 2016, FDA decided to maintain the safeguards while simultaneously approving an expansion of Mifeprex's indication, as requested by Mifeprex's sponsor, and relaxing other aspects of the drug's risk evaluation and mitigation strategy ("REMS"). The Agency made its expert decision to maintain the REMS's safeguards because it determined that Mifeprex's safety profile had not substantially changed since the drug was first approved—a decision based on information submitted by Mifeprex's sponsor and years' worth of data and experience.

Plaintiffs nevertheless ask this Court to override FDA's conclusion that the REMS's safeguards remain necessary to ensure patient safety. Specifically, Plaintiffs contest FDA's retention of three elements to assure safe use ("ETASU"),

which require that: (1) a certified health care provider dispense Mifeprex only in certain health care settings; (2) the health care provider complete a one-time prescriber agreement attesting to the provider's skills; and (3) the patient sign a form concerning administration of the drug.

FDA's decision to maintain these elements was a quintessentially scientific determination within the Agency's sound judgment. It also was supported—not undermined—by the fact that millions of women have used the drug without experiencing serious patient complications since FDA first put the safeguards in place. This record demonstrates that the safeguards are working and counsels in favor of retaining them. Plaintiffs have also failed to identify any scientific evidence that Mifeprex would remain safe for patient use in the absence of the REMS's safeguards. Indeed, Mifeprex's own sponsor did not challenge the continued value of the REMS's safeguards or request their elimination in 2015 when it sought other modifications.

Plaintiffs wrongly contest FDA's decision to retain the REMS's safeguards through quibbles with the administrative record, inapt comparisons to other drugs, and unsupported claims of political interference. None of these assertions has merit. The Agency's decision is fully supported by the administrative record and consistent with governing law. It also is constitutional, as imposing reasonable

restrictions on Mifeprex's dispensing is necessary to mitigate the drug's serious patient risks.

At root, Plaintiffs urge the Court to substitute its judgment for that of FDA on a highly technical matter within the Agency's expertise based on pure speculation about how patient safety might be affected by removing the REMS's safeguards. Law, facts, and good sense all argue against such a course. Scientific determinations regarding drug risks, and how best to protect patients against such risks, lie at the very center of FDA's experience and expertise, and it is for those very reasons that case law makes clear courts should not lightly second-guess such determinations. The Court should defer to the Agency's reasoned expertise, reject Plaintiffs' arguments, and grant summary judgment for FDA.

ARGUMENT

I. FDA's Decision to Retain the Mifeprex REMS Easily Satisfies the Administrative Procedure Act.

The scope of review under the Administrative Procedure Act ("APA") is "narrow" and does not permit a court to "substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). Under the "highly deferential" arbitrary-and-capricious standard, *Aguayo v. Jewell*, 827 F.3d 1213, 1226 (9th Cir. 2016), agency decisionmaking must be upheld so long as the agency "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action." *State Farm*, 463 U.S. at 43.

Even a "decision of less than ideal clarity" should be upheld if the decision was "based on a consideration of the relevant factors" and "the agency's path may reasonably be discerned." *Id.* (quoting *Bowman Transp., Inc. v. Ark.-Best Freight Sys., Inc.*, 419 U.S. 281, 285-86 (1974)).

APA review is particularly deferential in areas involving technical expertise and scientific judgment. *See, e.g.*, *Ranchers Cattlemen Action Legal Fund United Stockgrowers of Am. v. USDA*, 415 F.3d 1078, 1093 (9th Cir. 2005) ("Deference to the informed discretion of the responsible federal agencies is especially appropriate where, as here, the agency's decision involves a high level of technical expertise."). As the Supreme Court has explained, when reviewing "scientific determination[s], as opposed to simple findings of fact, a reviewing court must generally be at its most deferential." *Balt. Gas & Elec. Co. v. NRDC*, 462 U.S. 87, 103 (1983). FDA determinations regarding drug safety and risk management are quintessentially scientific judgments that fall at the very core of agency expertise and thus receive significant deference from reviewing courts. *See Aina Nui Corp. v. Jewell*, 52 F. Supp. 3d 1110, 1119 (D. Haw. 2014) ("Deference to the agency's technical expertise and experience is particularly important with respect to questions involving scientific matters.").

Contrary to Plaintiffs' contentions, FDA's reasons for maintaining the challenged REMS's safeguards are easily discernable and firmly rooted in data and

experience. This is more than enough to satisfy the APA's standard of review, particularly given the high level of deference this Court owes FDA's scientific judgments.

A. FDA's Decision to Retain the Mifeprex REMS Rested on Years of Safety Data and Agency Reviews Regarding Mifeprex's Safety Profile.

As an initial matter, Plaintiffs wrongly claim that FDA's 2016 REMS review is the "exclusive source for the Agency's rationale in reauthorizing the Mifeprex REMS in 2016," *see* Pls.' MSJ at 32 (citing JSF ¶ 50), and that the 2016 Review "contains *no* explanation, let alone a reasoned one," *id.* at 34 (emphasis added). To the contrary, as Plaintiffs stipulated, FDA's rationale for maintaining the Mifeprex REMS is set forth in *two* principal documents: FDA's 2013 REMS Review, JSF Ex. H, and FDA's 2016 REMS Review, JSF Ex. I. *See* JSF ¶ 50. Each document, in turn, references and relies on years of data and agency experience regulating Mifeprex since the drug's initial approval in 2000. The 2016 REMS Review, for example, explains that:

> During review of the efficacy supplement and proposed REMS Modifications, [FDA] evaluated the current REMS program to determine whether other changes were appropriate. As part of this evaluation, the review team took into consideration (1) the recent review of the Mifeprex REMS Assessment completed on October 13, 2015, (2) the addendum to the October 13, 2015 review completed on March 29, 2016, (3) safety data gathered over the past 16 years since approval, and (4) information regarding current clinical practice.

JSF Ex. I at 0702 (numbering added). Thus, the record contains years of data and multiple reviews that all support FDA's sound decision to retain the REMS restrictions in 2016. JSF Ex. I at 0681; *see also* JSF ¶¶ 50, 57; *see generally* JSF Exs. H, I.

B. FDA Reasonably Concluded That the Mifeprex REMS's Safeguards Remain Necessary to Ensure Patient Safety.

Plaintiffs assert that the Agency's decision to retain the three ETASU in the Mifeprex REMS was "patently irrational." Pls.' MSJ at 35. But FDA offered clear reasons for its decision, and Plaintiffs fail to present any evidence showing that FDA's determination was even incorrect, much less irrational. Plaintiffs provide no scientific evidence that safe patient use of Mifeprex can be achieved without the REMS's safeguards. Nor do they offer evidence that the drug's safety profile has "substantially changed" since it was first approved. This is unsurprising, because no such evidence exists. To the contrary, the data and information in the record, including from the Mifeprex clinical trials, support FDA's determination that the Mifeprex REMS mitigates patient risks associated with the drug, and that without the REMS, there might be an increase in serious patient complications. *See* JSF Ex. H at 0354; Defs.' Ex. 12 at 0223, 0226-27. This is more than enough to pass muster under the APA. *See State Farm*, 463 U.S. at 43 (agency decision should be upheld where agency "considered the relevant factors and articulated a rational connection between the facts found and the choice made"); *Ranchers Cattlemen*,

415 F.3d at 1093 (deference to agency decisionmaking is "especially appropriate where, as here, the agency's decision involves a high level of technical expertise").

1. FDA Reasonably Concluded That the Restricted Dispensing Requirement Mitigates Risks By Ensuring Patient Counseling at the Time of Dispensing.

Plaintiffs repeatedly claim that the REMS's dispensing requirement, which requires that a certified health care provider dispense Mifeprex only in certain health care settings, is irrational because, according to Plaintiffs, it does not mitigate the serious risks of infection and bleeding associated with Mifeprex.[1] *See, e.g.*, Pls.' MSJ at 35. But Plaintiffs ignore that this requirement ensures that Mifeprex is "dispensed under the direct supervision of a certified prescriber," Defs.' Ex. 20 at 0436; JSF Ex. I at 0681, thus allowing for counseling about the risk of serious patient complications associated with Mifeprex (and what to do if such complications arise) *at the time of dispensing*. JSF Ex. H at 0356-57. In this way, and as further explained *infra*, the restricted dispensing scheme rationally mitigates the serious patient risks associated with the use of Mifeprex.

Plaintiffs also assert that the restricted dispensing requirement is irrational because it eliminates the opportunity for "counseling from a pharmacist." Pls.'

[1] Plaintiffs also argue that there is "no evidence" that Mifeprex causes infection or bleeding. Pls.' MSJ at 7-8. Rather, Plaintiffs contend such complications, when they occur, are simply the result of "the patient's underlying pregnancy." *Id.* at 8. But it is undisputed that use of Mifeprex carries risks of sepsis and sometimes-life-threatening infections and bleeding. JSF ¶ 19.

MSJ at 35-36. But Plaintiffs present no evidence that counseling from a pharmacist is superior to counseling from a certified prescriber, and point to nothing in the record that undermines the Agency's conclusion that facilitating counseling by a certified prescriber at the time of dispensing helps mitigate patient risks.

Dispensing the drug in broader settings, such as through retail pharmacies, could also expose patients to unnecessary and increased risks. *See* JSF Ex. H at 0356. Patients might not, for example, receive proper counseling at the time of dispensing about the serious complications associated with Mifeprex or what to do if they experience such complications. *See id.* Patients might also delay picking up their Mifeprex prescription and initiating an abortion, resulting in increased risk. *See id.* Patients who have a hard time finding a pharmacy that stocks Mifeprex may similarly experience a delay with potential patient complications. *See id.* These reasonable concerns all support the Agency's decision to retain the restricted dispensing requirement.

Significantly, Plaintiffs ignore the fact that Mifeprex's sponsor, in submitting the supplemental new drug application ("sNDA") that led to FDA's 2016 review of the Mifeprex REMS, proposed only limited modifications to the existing REMS. Defs.' Ex. 20 at 0414-15, 0435. Plaintiffs thus ask this Court to

mandate changes to the Mifeprex REMS that Mifeprex's own sponsor did not even request.

FDA does not approve modifications to a drug's REMS absent an adequate rationale for the changes, including data to support the proposed changes. *See, e.g.*, REMS: Modifications and Revisions (Jul. 2019), Defs.' Ex. 39 at 12. Here, not only have Plaintiffs failed to identify any evidence demonstrating that Mifeprex would remain safe for patient use in the absence of the restricted dispensing requirement, but the evidence that does exist shows that Mifeprex's safety profile "ha[s] not substantially changed" since the drug was first approved with the restricted dispensing requirement in place. JSF Ex. I at 0681; *see also* JSF ¶¶ 50, 57; JSF Exs. H, I. FDA reasonably concluded that the restricted dispensing requirement helps mitigate the serious patient health risks associated with Mifeprex, and Plaintiffs point to no evidence that would justify overriding the Agency's considered judgment.

2. FDA Reasonably Concluded That the Prescriber Agreement Form Mitigates Risks by Requiring Prescribers to Attest to Certain Skills.

Plaintiffs also object to the requirement that prescribers of Mifeprex attest to certain skills, including, *inter alia*, the ability to: (1) perform surgical intervention or provide it through others; (2) date pregnancies accurately; and (3) diagnose ectopic pregnancies. *See* Pls.' MSJ at 36; *see also* Defs.' Ex. 12 at 0227; JSF Ex.

H at 0355-56. FDA, however, reasonably determined that these skills are necessary to ensure that prescribers of Mifeprex are "very familiar with managing early pregnancy," Defs.' Ex. 12 at 0227, thereby mitigating potential patient risks associated with the drug. Moreover, the required skills all relate to specific risks associated with Mifeprex, which is indicated only for pregnancies before a certain date, is contraindicated for ectopic pregnancies, and carries a risk of incomplete abortion and serious bleeding requiring surgical intervention in about 2-7 out of every 100 patients who use the drug. *See* JSF Ex. H at 0356. Without the Prescriber Agreement Form, prescribers also would not be required to report patient deaths associated with Mifeprex to the sponsor—a requirement that ensures the sponsor receives all reports of patient deaths and is able, in turn, and consistent with its regulatory obligations, to report those deaths to FDA. *See* Defs.' Ex. 22 at 0576. Thus, the Prescriber Agreement Form facilitates FDA monitoring of complications associated with Mifeprex's use. Defs.' Ex. 33 at 1-2; JSF Ex. C at 0405.

Plaintiffs argue that the Prescriber Agreement Form is unnecessary because prescribers are already governed by legal and ethical standards that require them to "prescribe drugs only if qualified to do so." Pls.' MSJ at 36; *see also* Pls.' Concise Stmt. of Facts ("PCSF") Ex. A ¶¶ 58, 67, 76 (Dkt. No. 87). But Plaintiffs cite no authority for the proposition that the existence of legal and ethical standards that

provide some safeguards prevents FDA from imposing the same or *additional* safeguards that, in the Agency's judgment, will mitigate patient risk. Nor do they explain what those undefined "legal and ethical standards"—which presumably vary by state—are, let alone how they think such standards apply here.

Plaintiffs' argument, if accepted, would also prevent FDA from *ever* adopting REMS restrictions that require prescribers to attest to certain skills or expertise, as the legal and ethical standards Plaintiffs allude to would always limit the universe of available prescribers to those "qualified" to prescribe a particular drug. Plaintiffs again cite no authority for such a dramatic limitation on FDA's ability to mitigate patient risk, a limitation that runs wholly contrary to the entire purpose of granting FDA authority to require a REMS in the first place.

Plaintiffs also assert that the Prescriber Agreement Form is arbitrary and capricious because "[v]irtually any clinician caring for pregnant patients can date and diagnose a pregnancy," and any clinician "not comfortable doing so can obtain that information by ordering an ultrasound." Pls.' MSJ at 22. Even if many clinicians caring for pregnant women are able to date and diagnose an intrauterine pregnancy, however, Plaintiffs cite no evidence showing that all, or nearly all, such clinicians are also able to diagnose an ectopic pregnancy—a critical skill required of prescribers to ensure safe patient use of Mifeprex. *See* JSF Ex. H. at 0355, 0359. Plaintiffs also cite no evidence that, without the Prescriber Agreement

Form, prescribers who do not know how to date a pregnancy or diagnose an ectopic pregnancy will take the extra step of ordering an ultrasound. There was nothing unreasonable about FDA's conclusion that requiring prescribers to attest that they know how to date a pregnancy will mitigate the patient risks associated with Mifeprex.

Plaintiffs lodge two final complaints against the Prescriber Agreement Form: (1) all clinicians are able to direct a patient to the nearest emergency department; and (2) all clinicians with prescribing authority can read and understand the Mifeprex prescribing information. Pls.' MSJ at 22. These complaints misstate the elements of the Prescriber Agreement Form and also misunderstand its purpose. *First*, the Prescriber Agreement Form does not state that a prescriber merely be able to "direct a patient to the nearest emergency department." Rather, prescribers must agree that they are able to provide surgical intervention themselves or arrange it through others if necessary. Defs.' Ex. 12 at 0227; JSF Ex. H at 0355-56. This requirement helps protect patient safety in the event of an incomplete abortion. JSF Ex. H. at 0357. Plaintiffs provide no evidence that "direct[ing] a patient to the nearest emergency department" mitigates patient risk as effectively as providing surgical intervention directly or arranging it through others.

Second, even if all clinicians were able to read and understand the Mifeprex prescribing information—and Plaintiffs provide no evidence that this is the case—

being able to read and understand the prescribing information is a far cry from having the requisite knowledge and skill regarding early pregnancy. As discussed, a critical part of the Prescriber Agreement Form is ensuring that prescribers are knowledgeable about early pregnancy so that they can easily date pregnancy, diagnose ectopic pregnancies, and provide surgical interventions in the event of an incomplete abortion. FDA reasonably concluded that the skills articulated in the Prescriber Agreement Form mitigate the patient risks associated with the drug's use. Plaintiffs point to no scientific evidence that undermines this conclusion and, again, improperly ask the Court to substitute its judgment for the Agency's technical expertise.

3. FDA Reasonably Concluded That the Patient Agreement Form Mitigates Risks by Ensuring Proper Patient Counseling.

Plaintiffs next claim that FDA's decision to retain the Patient Agreement Form was arbitrary and capricious because FDA's scientific review team recommended removing the Form and because the Form was retained, according to Plaintiffs, "without a shred of supporting evidence." Pls.' MSJ at 36. In making these claims, however, Plaintiffs disregard both the rationale behind FDA's ultimate conclusion to retain the Form and the high level of deference that conclusion is owed. Although FDA reviewers initially recommended removal, FDA chose to retain the Form because doing so "would not interfere with access

and would provide additional assurance that the patient is aware of the nature of the procedure, its risks, and the need for appropriate follow-up care." Compl. Ex. D at 1.

The Agency's 2016 conclusion to retain the Form was consistent with its rationale for including the Patient Agreement when Mifeprex was approved in 2000. At that time, FDA noted the importance of the Patient Agreement in furthering the goals of patient safety, including by informing patients "about the indication of the drug and how it is given," helping them "understand the type of regimen they are about to commit to and its risks and benefits," and encouraging "active participation" in the treatment process. Defs.' Ex. 12 at 0225, 0230. Indeed, one of FDA's chief reasons for requiring the Patient Agreement in 2000 was to ensure that "women are completely informed about the process and make a commitment to follow through." *Id.* FDA accordingly required patients not only to review the form with the prescriber, but also to sign it, and instructed prescribers to provide patients with a copy to take home and use as a reference. *Id.* Thus, it is not surprising that, in 2016, the Agency determined that retaining the Patient Agreement Form was necessary to mitigate patient risk.

Plaintiffs further contend that FDA acted in bad faith in light of the FDA Commissioner's involvement in the 2016 REMS review. Pls.' MSJ at 37-39. But this assertion has no support in the record. During the 2016 REMS review, the

FDA Commissioner provided input on a single ETASU—the Patient Agreement Form—and, out of concern for patient safety, requested that it be retained. There was nothing inappropriate about this request. The Commissioner was a medical doctor appointed by the President and confirmed by the Senate to lead the federal agency charged with evaluating and ensuring drug safety. The Commissioner was briefed on the matter and engaged as he would on any other Agency decision. Plaintiffs provide no evidence at all—not even a scintilla—that the Commissioner acted with improper motives or that his role was in any way inappropriate.

Plaintiffs attempt to bolster their argument by likening this case to *Tummino v. Torti*, 603 F. Supp. 2d 519 (E.D.N.Y. 2009). But unlike *Tummino*, there is no evidence here that "the Commissioner—at the behest of political actors—[made his decision] before FDA scientific review staff had completed their reviews." *See id.* at 524. Likewise, there is no suggestion that anyone outside the Agency pressured the Commissioner or that the Commissioner "transmitted this pressure down the chain of command at the FDA." *See id.* at 546. Nor did the Commissioner's request represent a departure from FDA's policies with respect to REMS evaluations. Moreover, the authority the Agency exercises when imposing REMS requirements is authority that the Secretary of HHS has delegated *to the Commissioner*. *See* 21 U.S.C. § 393(d)(2); FDA Staff Manual Guides

§§ 1410.10(1)(A)(14), 1410.21(1)(A); *see also* 21 C.F.R. §§ 10.25(b), 10.33(a); 21 U.S.C. § 355-1.

And, perhaps most importantly, the request was consistent with years of Agency determinations regarding the importance of the Patient Agreement Form in mitigating patient risk. In all events, "a court may not set aside an agency's policymaking decision solely because it might have been influenced by political considerations or prompted by an Administration's priorities." *Dep't of Commerce v. New York*, 139 S. Ct. 2551, 2573 (2019). There was nothing arbitrary or capricious about FDA's decision to retain the Patient Agreement Form.

4. Plaintiffs' Comparisons to Other Drugs Do Not Establish That the Mifeprex REMS Is Unlawful.

Plaintiffs rely on 21 U.S.C. § 355-1(f)(2)(D)(i) to argue that Mifeprex should not have a REMS because other drugs with serious risks lack a REMS. But, as explained more fully below, section 355-1(a)(1) does not apply to drugs such as Mifeprex that have a "deemed" REMS—that is, restrictions that predate enactment of the Food and Drug Administration Amendments Act of 2007 ("FDAAA"). *See* Section I.C, *infra*. And even were it applicable, section 355-1(f)(2)(D)(i) does not require the Agency to compare the REMS for one drug with another, assigning greater restrictions to drugs with greater risks. Instead, as FDA explained in its 2019 REMS Guidance, the Agency is required look at each drug independently, assessing each drug's risks in comparison to that same drug's

benefits. *See* Defs.' Ex. 35 at 4. FDA's assessment is individualized, and comparisons across drugs are virtually meaningless. *See id.* FDA's assessment is also highly technical and scientific—the sort of decision for which deference is "especially appropriate." *Ranchers Cattleman*, 415 F.3d at 1093. It is certainly not the realm for a court to "substitute its judgment" for that of the Agency. *State Farm*, 463 U.S. at 43.

In any event, Plaintiffs' comparison to Korlym, an FDA-approved drug that shares the same active ingredient as Mifeprex, mifepristone, is inapt. Plaintiffs wrongly argue that because Korlym contains mifepristone and does not have a REMS, Mifeprex likewise should not have a REMS. But while Korlym and Mifeprex indeed share the same active ingredient, they have very different approved indications and patient populations. *See* Defs.' Ex. 14, 15, 16. As FDA explained in declining to require a REMS for Korlym, "[t]he agency evaluates an active ingredient based on the risk benefit profile *for the intended population*." Defs.' Ex. 15 at 0301 (emphasis added).

Korlym is indicated "to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery." Defs.' Ex. 14 at 0271. Cushing's syndrome is an extremely rare and sometimes fatal disease. *See* Defs.' Ex. 15 at 0296-97 (noting

that there are only 20,000 Cushing's syndrome patients in the United States at any given time, only 5,000 of whom are candidates for Korlym). As FDA explained, the "hypercortisolemic state of [Cushing's] patients often results in . . . infertility," and "[c]hronic therapy of mifepristone at the doses necessary to control hypercortisolemia is also an effective contraceptive." Defs.' Ex. 16 at 0328. For both these reasons, FDA concluded that "the probability that a Cushing's patient will become pregnant while on Korlym is very low." *Id.*; *see also* Defs.' Ex. 15 at 0304.

Under these circumstances, FDA reasonably concluded that the risks to Korlym patients from administering mifepristone could be managed through labeling—such as contraindicating administration of Korlym for patients who are pregnant, Defs.' Ex. 14 at 0269—and that a REMS was not necessary, *see id.* at 0271 (Korlym labeling with a boxed warning and a contraindication for women who are pregnant). As FDA explained, a REMS with ETASU was "not necessary to ensure that the benefits outweigh the risks of Korlym *in the Cushing's population*," and "would not improve the benefit/risk balance for the intended use (Cushing's) population and would add burden." Defs.' Ex. 15 at 0294 (emphasis added). Obviously, FDA could not take the same approach with Mifeprex—contraindicating the drug for patients who are pregnant—given that this is the intended patient population for Mifeprex.

Plaintiffs' comparisons to misoprostol and warfarin fare no better when properly viewed in light of those drugs' intended uses and patient populations. Misoprostol is "indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)–induced gastric ulcers in patients at high risk of complications from gastric ulcer."[2] And warfarin is a very old and widely prescribed anticoagulant.[3] Health care practitioners and patients have long understood how to manage the risks of anticoagulants such as warfarin. Those indications and histories of experience have no bearing on the Agency's assessment of Mifeprex, which as discussed, carries its own safety risks in light of its intended use in terminating early pregnancy.

Far from demonstrating disparate treatment of like drugs, the examples of other drugs Plaintiffs point to instead illustrate how FDA properly considers each drug on its own terms. The APA requires no more.[4]

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[2] *See* Cytotec, misoprostol tablets, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019268s051lbl.pdf (last visited Jan. 10, 2020).

[3] *See* Douglas Wardrop, David Keeling, *The Story of The Discovery of Heparin And Warfarin*, 141 BRITISH J. HAEMATOLOGY, 757, 759-62 (2008), *available at* https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1365-2141.2008.07119.x (last visited Jan. 10, 2020).

[4] *Bracco Diagnostics v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997), does not require a different result. In *Bracco*, FDA sought to regulate "functionally indistinguishable" products differently (one as a drug and the other as a device), despite their identical intended uses. *Id.* at 24, 28. Here, by contrast, Mifeprex and Korlym have wholly distinct indications and intended uses for wholly different patient populations.

C. FDA Complied With Applicable Statutory Requirements in Imposing (and Retaining) the Mifeprex REMS.

Plaintiffs further contend that FDA's decision to impose (and retain) the Mifeprex REMS's requirements exceeded FDA's statutory authority. In particular, Plaintiffs fault FDA for allegedly failing to examine the six benefit/risk factors set out in 21 U.S.C. § 355-1(a)(1) and allegedly disregarding the prohibition on ETASU's that are "unduly burdensome on patient access," in 21 U.S.C. § 355-1(f)(2)(C). These claims are meritless. Mifeprex was approved in 2000, long before these statutory requirements took effect. And there is no indication that Congress, upon enacting FDAAA, intended to retroactively apply these specific REMS-related provisions in that Act to "deemed" REMS requirements that pre-dated enactment of the statute.

As Plaintiffs acknowledge, FDA regulations in effect at the time of Mifeprex's approval in 2000 permitted the Agency to require, under certain circumstances, restrictions necessary "to assure safe use of the drug product." 21 C.F.R. § 314.520 ("Subpart H"). Upon FDAAA's passage in 2007, drug products with restrictions necessary to assure safe use that were previously approved under Subpart H were "deemed" to have an approved REMS in effect. FDAAA, Pub. L. No. 110-85, § 909(b)(1), 121 Stat. 823, 951 (2007). Notably, however, FDAAA did not require retroactive review or reevaluation of whether a deemed REMS satisfied each of FDAAA's new statutory requirements.

FDAAA also did not mandate the reevaluation of a deemed REMS according to FDAAA's new statutory requirements whenever a deemed REMS is modified in the future. Although a sponsor may submit proposed changes to a REMS, or FDA may require changes to "(i) ensure the benefits of the drug outweigh the risks of the drug; or (ii) minimize the burden on the health care delivery system of complying with the strategy," 21 U.S.C. § 355-1(g)(4)(B), Congress did not require FDA to examine (or re-examine) the statutory factors under section 355-1(a)(1) in the course of considering such modifications. *See* 21 U.S.C. § 355-1(g). Nor did Congress require an analysis of burdens on patient access under section 355-1(f)(2). *See id.*

Thus, contrary to Plaintiffs' suggestion, FDA had no statutory or regulatory obligation to consider the statutory factors in section 355-1(a)(1) or undertake the burden analysis in section 355-1(f)(2)(C) when it decided to retain the Mifeprex REMS. Because Mifeprex was initially approved with restrictions pursuant to Subpart H, and subsequently had a "deemed" REMS, section 355-1(a)(1) is inapplicable. FDA complied with all applicable authority governing deemed REMS and acted well within its statutory authority in retaining Mifeprex's pre-FDAAA restrictions.

II. FDA is Entitled to Summary Judgment on Plaintiffs' Constitutional Claims.

A. Plaintiffs Fail to Establish a Due Process Violation.

As the Supreme Court has made clear, the fact that a law has the "incidental effect of making it more difficult or more expensive to procure an abortion cannot be enough to invalidate it." *Planned Parenthood of Se. Penn. v. Casey*, 505 U.S. 833, 874 (1992) (joint opinion). Instead, to establish a due process violation under the Supreme Court's precedents, Plaintiffs must show that the Mifeprex REMS imposes an "undue burden" on abortion access. *Id.* And in the Ninth Circuit, a law imposes an undue burden only if, "in a large fraction of the cases in which [the law] is relevant, it will operate as a substantial obstacle to a woman's choice to undergo an abortion." *Planned Parenthood Ariz., Inc. v. Humble*, 753 F.3d 905, 914 (9th Cir. 2014). Even assuming that the Mifeprex REMS affects abortion access, Plaintiffs fail to meet this standard.[5]

[5] Although the Ninth Circuit employs a large-fraction formulation in adjudicating facial challenges to abortion laws, the proper standard remains an "open question" in the Supreme Court. *Whole Woman's Health v. Hellerstedt*, 136 S. Ct. 2292, 2343 n.11 (2016) (Alito, J., dissenting). The government acknowledges that this Court must apply the large-fraction standard under Ninth Circuit precedent, but disagrees with that standard and preserves this issue for further review. There is no basis for carving out an abortion exception to the general rule—which Plaintiffs make no attempt to meet—that a law is facially unconstitutional only if "no set of circumstances exists under which the Act would be valid." *United States v. Salerno*, 481 U.S. 739, 745 (1987); *see* U.S. Amicus Brief, *June Medical Servs. v. Gee*, Nos. 18-1323 & 18-1460 (Jan. 2, 2020), at 29-30.

1. The Mifeprex REMS is Not a Substantial Obstacle to a Large Fraction of Women Seeking Medication Abortion.

Plaintiffs claim that the Mifeprex REMS burdens abortion access by: (1) reducing where medication abortion is available; (2) delaying access to time-sensitive care; (3) increasing costs to low income women who must travel to see a certified prescriber; and (4) exposing women to the risks of pregnancy and childbirth if they cannot reach a clinician who can prescribe Mifeprex. Pls.' MSJ at 40-41. But even assuming the Mifeprex REMS incidentally affects access to abortion, Plaintiffs have not shown that the Mifeprex REMS is a "substantial obstacle" to a large fraction of women seeking medication abortion. *See Humble*, 753 F.3d at 912.

Since 2000, millions of women have taken Mifeprex for medication abortion, *see* JSF ¶ 21, demonstrating that the REMS has *not* been a substantial obstacle. Instead, the Mifeprex REMS has permitted approval of an abortion drug that would not otherwise be available. Prior to FDA's approval of Mifeprex, nearly all first-trimester abortions were surgical. *See Planned Parenthood Sw. Ohio Region v. Dewine*, 696 F.3d 490, 494 (6th Cir. 2012). By mitigating the risks associated with Mifeprex, the restrictions that later became the REMS allowed FDA to approve Mifeprex for medication abortion. *See* JSF Ex. H at 0354-55. And, since its approval, FDA has approved modifications that lessened restrictions on Mifeprex by allowing certain nonphysicians to prescribe it (if they meet the

certification requirements), allowing the drugs to be taken outside of a prescriber's office, and reducing restrictions on follow-up visits. *See* Defs.' Ex. 20 at 0414-38.

Importantly, Plaintiffs have not established a causal connection between their asserted burdens and the Mifeprex REMS. *See Hellerstedt*, 136 S. Ct. at 2313 (discussing petitioners' burden to present evidence of causation). Instead, Plaintiffs complain of many other obstacles to abortion access, including indigency, drug-formulary requirements at hospitals, opposition to abortion, and fear of harassment or violence caused by stocking and dispensing Mifeprex. *See, e.g.*, PCSF Ex. C ¶¶ 9-16, Ex. E ¶¶ 17-52, Ex. G ¶ 8, Ex. H ¶ 10, Ex. I ¶¶ 7-14, Ex. J ¶¶ 11-14. But these obstacles would exist even if Mifeprex were *not* subject to a REMS. *See Casey*, 505 U.S. at 885-87 (rejecting argument regarding 24-hour waiting period that increased risk of harassment and impact on indigent women constituted substantial obstacles); *cf. Harris v. McRae*, 448 U.S. 297, 316 (1980) ("Although government may not place obstacles in the path of a woman's exercise of her freedom of choice, it need not remove those not of its own creation."). For example, if the restricted-dispensing requirement were removed, women might experience similar obstacles to abortion access, as pharmacies could refuse to stock and dispense Mifeprex because of opposition to abortion or fear of harassment or violence. *See* JSF Ex. H at 0356 (discussing potential difficulties obtaining

Mifeprex from pharmacies if REMS removed); JSF Ex. F at 1266 (discussing pharmacy refusal laws).

Even assuming the Mifeprex REMS is an obstacle for some women, Plaintiffs have not established that it is a "substantial obstacle" to a "large fraction" of women seeking medication abortion. *See Humble*, 753 F.3d at 914. Plaintiffs fail to identify the number of women seeking medication abortion for whom the Mifeprex REMS is a substantial obstacle, much less show that such number is a large fraction of women who seek abortion. *Cf. Cincinnati Women's Servs. v. Taft*, 468 F.3d 361, 372-73 (6th Cir. 2006) (holding that in-person requirement preventing 12 out of 100 women from obtaining abortion not large fraction); *Planned Parenthood Ark. & E. Okla. v. Jegley*, No. 4:15-cv-00784-KGB, 2018 WL 3029104, at *16 (E.D. Ark. June 18, 2018) (holding that contract-physician requirement burdened 100% of women seeking medication abortions in Arkansas). For example, Plaintiffs contend that 39% of women of reproductive age do not have an abortion provider within their county, *see* PCSF Ex. E ¶¶ 6, 47, but Plaintiffs have not shown how many of these women might seek medication abortion yet face substantial obstacles in doing so because of the Mifeprex REMS.

That women may incur increased travel expenses to see a certified prescriber in some states, such as Hawaii, does not render the burden "undue." *See Hellerstedt*, 136 S. Ct. at 2313 (noting that "[i]ncreased driving distances do not

always constitute an 'undue burden'"); *Casey*, 505 U.S. at 885-87 (rejecting argument that increased travel costs of 24-hour waiting period amounted to a substantial obstacle). Further, Plaintiffs also fail to identify the number of women for whom travel to a certified prescriber is a burden. Even for women who must travel to a certified prescriber, the Mifeprex REMS requires that the prescriber dispense the drug directly to the patient. *See* JSF Ex. H at 0358. Put simply, increased travel costs are "incidental effects" of the Mifeprex REMS that do not create a substantial obstacle to obtaining an abortion for a large fraction of women seeking one (let alone all such women) and therefore do not constitute an undue burden on abortion access. *See Casey*, 505 U.S. at 874.

2. The Benefit of the Mifeprex REMS in Mitigating Patient Risks Outweighs any Incidental Burdens on Abortion Access.

Even if Plaintiffs had shown that the Mifeprex REMS imposes a "substantial obstacle to a woman's choice to undergo an abortion" in "a large fraction of the cases in which [the law] is relevant," *Humble*, 753 F.3d at 914, their challenge would still fail because they have not shown that any burdens created by the law outweigh the substantial benefit of the REMS in mitigating serious patient risks.

To start, FDA has determined that the Mifeprex REMS is necessary to mitigate serious risks associated with the drug's use. *See supra* at 6-16; *see also supra* at 4-7, 16-17 (noting high degree of deference owed to agency's scientific

determinations). Importantly, the record lacks any evidence from clinical trials showing that the Mifeprex REMS is unnecessary for patient safety. *See Humble*, 753 F.3d at 909 (noting that when FDA approves a drug, "it does so on the basis of evidence of clinical trials submitted by the drug's manufacturer"). By contrast, the record contains an abundance of data and information (including from the Mifeprex clinical trials) supporting FDA's determination that the Mifeprex REMS is necessary and that, without it, there might be an increase in serious patient complications. *See supra* at 6. The Mifeprex REMS thus furthers FDA's legitimate interest in ensuring patient safety. *See Casey*, 505 U.S. at 878 (holding that state may enact abortion regulations to further maternal health and safety); *Tucson Woman's Clinic v. Eden*, 379 F.3d 531, 539 (9th Cir. 2004) (noting legitimate interest in maternal health).

Relying on an unsupported statement in a declaration, Plaintiffs assert that the Mifeprex REMS "provides no medical benefit." PCSF Ex. A. ¶ 83. Specifically, Plaintiffs argue that requiring Mifeprex to be dispensed only in certain health care settings is "illogical" because the patient can take the pill at home, and any adverse event "would not occur until hours or days later." *Id.* ¶¶ 48, 50, 53. This assertion is incorrect for several reasons.

As an initial matter, the ramifications of Plaintiffs' argument here are quite far-reaching—and deeply problematic. According to Plaintiffs, because FDA in

2016 eased restrictions on where patients can *take* Mifeprex, FDA is required to also ease restrictions on where patients can *obtain* Mifeprex. But there is no reason in law or logic why FDA should be required to ease restrictions on taking and restrictions on obtaining a drug in tandem, particularly where (as here) the sNDA that prompted the Agency's review did not request changes to both. *See* Defs.' Ex. 20 at 0414-415, 0435. FDA can reasonably ease (or even strengthen) one restriction while leaving the other in place. There is no reason to subject FDA to the sort of regulatory straitjacket Plaintiffs seek to foist upon the Agency.

Moreover, as discussed *supra*, Plaintiffs misstate the purpose of the restricted dispensing scheme, which is to ensure that, at the time of dispensing, the patient will receive counseling about the risk of serious patient complications associated with Mifeprex. *See supra* at 7-8. And, as Plaintiffs acknowledge, Pls.' MSJ at 12-13, FDA permitted home use of Mifeprex and misoprostol only after reviewing data supporting its safety; it was not "illogical" for FDA to take this step without going as far as Plaintiffs would have preferred and removing the restricted dispensing requirement entirely.

Plaintiffs also challenge the necessity of the Prescriber and Patient Agreement Forms, claiming they are duplicative of clinical, ethical, and legal standards already governing clinicians. PCSF Ex. A ¶¶ 58, 67, 76. However, as discussed *supra*, Plaintiffs cite no authority for the proposition that the existence of

clinical, ethical, and legal standards prevents FDA from imposing the same or *additional* safeguards that will mitigate patient risk. *See supra* at 10-11. Nor do they explain which clinical, ethical, and legal standards should apply here. *See id.* Contrary to Plaintiffs' assertion, the Prescriber and Patient Agreement Forms are necessary to mitigate the patient risks associated with Mifeprex as described in Sections I.B.2 & 3, *supra*.

Plaintiffs rely on *Hellerstedt* and *Humble* to support their undue burden claim, but, unlike the Mifeprex REMS, the challenged laws in those cases (according to the reviewing courts) imposed substantial obstacles on abortion access and failed to further a legitimate safety interest. *See* Pls.' MSJ at 40-41. In *Humble*, the Ninth Circuit struck down an Arizona abortion law because it concluded the law substantially burdened abortion access by, *inter alia*, effectively banning medication abortions for a "significant number of women," and that the law was "wholly unnecessary as a matter of women's health." *Humble*, 753 F.3d at 915-16 (internal quotations and citation omitted). Similarly, the Supreme Court in *Hellerstedt* invalidated admitting-privileges and other health-standards requirements for abortion clinics because it concluded that the record indicated that many clinics had closed as a result of the law, producing a substantial obstacle to obtaining an abortion for a large fraction of Texas women seeking one, and that there was no record evidence showing the requirements "advanced Texas'

legitimate interest in protecting women's health." *Hellerstedt*, 136 S. Ct. at 2311-12. Here, by contrast, there is no evidence that the Mifeprex REMS imposes such burdens on abortion access, and FDA has determined, based on ample evidence, that the REMS is necessary to ensure patient safety. *See, e.g.*, JSF Ex. H at 0344.

B. Plaintiffs Fail to Establish an Equal Protection Violation.

Plaintiffs claim that the Mifeprex REMS violates equal protection by treating Plaintiffs and their members differently from clinicians providing comparable medications. Pls.' MSJ at 41-42. In assessing equal-protection challenges, the Ninth Circuit applies rational basis review to laws impacting abortion providers. *Eden*, 379 F.3d at 544-47. "A law will survive rational basis review 'so long as it bears a rational relation to some legitimate end'" and there is no "stigmatizing or animus based purpose to the law." *Id.* at 543, 546.

Here, Plaintiffs lack any support for their assertion that the Mifeprex REMS is the result of a stigmatizing purpose or animus. On the contrary, the Mifeprex REMS seeks to mitigate the undeniably serious risks associated with the use of Mifeprex. Moreover, as discussed above, FDA has equally rational reasons for treating Mifeprex and Korlym differently. As such, Plaintiffs' equal protection claim cannot survive rational basis review.

1. The Mifeprex REMS is Rationally Related to Patient Safety.

The Mifeprex REMS bears a manifestly rational relationship to patient safety. As discussed *supra*, FDA determined that the Mifeprex REMS is necessary to mitigate serious risks to the patients who take Mifeprex, including infection, bleeding, and death. *See supra* at 6-16; JSF Ex. H at 0344, 0356-57, Ex. I at 0681-82. As FDA has explained, if the Mifeprex REMS were eliminated, there might be an increase in serious patient complications. *See supra* at 6.

That the REMS impacts prescribers of Mifeprex differently from prescribers of Korlym also does not render the Mifeprex REMS "irrational." *See* Pls.' MSJ at 41. FDA has a rational basis for treating these drugs differently—they have distinctly different approved indications, patient populations, and risks. *See supra* at 16-19. Thus, the Mifeprex REMS is "facially related to health and safety issues." *See Eden*, 379 F.3d at 546 (upholding law impacting abortion providers under rational basis review).

2. Plaintiffs Fail to Demonstrate an Illegitimate Purpose.

Plaintiffs further argue that the Mifeprex REMS rests on allegedly impermissible motives, "as evidenced by the Commissioner's highly unusual interference with the Mifeprex REMS." Pls.' MSJ at 41-42. But the record lacks any evidence of a "stigmatizing or animus based purpose" behind the Mifeprex REMS. *See Eden*, 379 F.3d at 546. By contrast, the record reflects that the FDA

Commissioner's chief concern was patient safety. *See supra* at 13-16. Likewise, Plaintiffs have no support for their remarkable assertion that an FDA Commissioner cannot provide input during the REMS review process. *See id.*

Plaintiffs rely on *City of Cleburne* and *Plyler* in support of their equal protection claim, but these cases are nowhere near on point. Pls.' MSJ at 41-42. In *City of Cleburne*, the Supreme Court invalidated a zoning ordinance under rational basis review where the permit requirement rested "on an irrational prejudice against the mentally retarded." *City of Cleburne, Tex. v. Cleburne Living Ctr.*, 473 U.S. 432, 450 (1985). Similarly, in *Plyler*, the Supreme Court invalidated a law denying public education to unlawfully present children after the Court concluded there was no substantial state interest. *Plyler v. Doe*, 457 U.S. 202, 228-30 (1982). By contrast, the Mifeprex REMS has a legitimate purpose of ensuring patient safety, and there is nothing in the record even remotely suggesting that the FDA Commissioner acted with impermissible motives.

CONCLUSION

For all the foregoing reasons, the Court should deny Plaintiffs' motion for summary judgment and grant judgment in favor of Defendants.

Dated: January 10, 2020

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CERTIFICATION

I certify using the word count feature of Microsoft Word, that the above memorandum in opposition to Plaintiffs' cross-motion for summary judgment consists of 7,451 words, below the 7,500-word limit requested by the parties (Dkt. No. 79) (granted in part by Dkt. No. 82).

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*, Plaintiffs, v. ALEX M. AZAR, II, M.D., M.P.H., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*, Defendants.	CIV. NO. 1:17-00493 JAO-RT **CERTIFICATE OF SERVICE**

I hereby certify that, on the dates and by the methods of service noted below, a true and correct copy of the foregoing was served on the following:

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