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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 **DEFENDANTS' CONCISE STATEMENT IN RESPONSE TO PLAINTIFFS' CONCISE STATEMENT OF FACTS (DKT. NO. 87)**

Pursuant to Rule LR56.1(e) of the Local Rules of Practice for the United States District Court for the District of Hawai‘i, Defendants Secretary Alex M. Azar II, Acting Commissioner Brett Giroir, and United States Food and Drug Administration ("FDA"), by and through counsel, hereby submit their concise statement in response to Plaintiffs' Concise Statement of Facts, Dkt. No. 87, in support of Plaintiffs' Motion for Summary Judgment, Dkt. No. 86.

#	**PLAINTIFFS' STATEMENT OF FACT**	**DEFENDANTS' RESPONSE AND SOURCE**
1	Unwanted pregnancy "can be a serious medical condition" causing, *e.g.*, "life- threatening hemorrhage" and "depression [and] anxiety." Administrative Record ("AR") 0859-60 (2016).	Not disputed.
2	The FDA regimen for medication abortion involves: (1) *mifepristone* (Mifeprex®), which blocks the effect of progesterone, a hormone necessary to maintain pregnancy, and (2) *misoprostol* (Cytotec®), which causes contractions and bleeding that empty the uterus. Decl. of Courtney Schreiber, M.D., M.P.H. attached as Ex. A, at ¶¶10, 13-16, 40-41.	Not disputed except that the approved regimen involves misoprostol, without reference to any brand name.
3	Mifeprex is "important to the health of women," providing a "meaningful therapeutic benefit" over surgical abortion for some	Not disputed that AR 0226 states: "The drug product [Mifeprex] is important to the health of women and the Medication Guide will encourage patient adherence to directions for

	patients. AR 0226, 0228 (2000), 0860 (2016).	use;" that AR 0228 states: "The meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure;" and that AR 0860 states: "Furthermore, consistent with § 314.500, medical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion."
4	Since 2000, Mifeprex "has been increasingly used as its efficacy and safety have become well-established by both research and experience, and serious complications have proven to be extremely rare." AR 0539 (2016).	Not disputed.
5	By October 2012, Mifeprex had been used nearly 2 million times in the United States. JSF Ex. H, at 0351.	Not disputed.
6	Today, medication abortion accounts for 39% of U.S. abortions. Schreiber ¶12.	Not disputed that according to the source cited in Schreiber ¶ 12 (https://www.guttmacher.org/report/abortion-incidence-service-availability-us-2017), 39% was for 2017. According to the CDC, 28% of all abortions at 8 weeks or less gestation were nonsurgical in 2016. https://www.cdc.gov/mmwr/volumes/68/ss/ss6811a1.htm. Disputed in that the fact is not material to this case.

7	No new safety concerns for Mifeprex have been identified since 2005. JSF Ex. H, at 0354; AR 0535.	Not disputed.
8	Adverse events among Mifeprex users are "exceedingly rare, generally far below 0.1% for any individual adverse event." AR 0574 (2016).	Not disputed that "*Major* adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are reported rarely in the literature on over 30,000 patients. The rates, when noted, are exceedingly rare, generally far below 0.1% for any individual adverse event." AR 0574 (emphasis added). Disputed as to adverse events more generally. "About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness." JSF Ex. A at 0389. *See also* AR 0387 ("Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. . . Up to 8% of all subjects may experience some type of bleeding for 30 days or more. . . . Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions."); *see also* JSF Ex. A at 0399 ("About 2

		to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.").
9	The serious adverse events listed in Mifeprex's labeling are "Serious and sometimes fatal infections or bleeding." JSF¶19 & Ex. A, at 0383.	Not disputed that "Serious and sometimes fatal infections or bleeding" is the heading for the boxed warning on the Mifeprex labeling. Disputed to the extent it is suggested that those are the only serious adverse events that may be associated with Mifeprex. *See, e.g.*, AR 0578 ("The nonfatal serious adverse events typically discussed in the literature are hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy.").
10	The FDA acknowledges that the same risks of infections and bleeding exist any time the pregnant uterus is emptied. *See* JSF ¶19 & Ex. A, at 0383-84, 0387, 0398.	Disputed. The Mifeprex boxed warning mentions risks associated with "spontaneous, surgical, and medical abortions" but does not characterize risks as "the same." JSF Ex. A at 0384. "*Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions." JSF Ex. A at 0387. "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." JSF Ex. A at 0398.

		Disputed in that the fact is not material to this case.
11	The risk of death associated with pregnancy and childbirth is approximately 14 times higher than that of abortion. Schreiber ¶9.	Not disputed that the cited study reports that data from 1998-2005. Schreiber ¶ 9. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
12	"[T]he physiology of pregnancy may be a more plausible risk factor" than Mifeprex for any rare infections following use. AR 0881 (2016).	Not disputed as to *C. sordellii* infection only: "The fact that cases of *C. sordellii* have been identified both in pregnant women who have undergone medical abortion and those who have not supports the idea that the physiology of pregnancy may be a more plausible risk factor for *C. sordellii* illness than having undergone a medical abortion with Mifeprex." AR 0881 at n.69. Disputed as to any other possible infections, and disputed in that the fact is not material to this case.
13	Even with chronic use, mifepristone is associated with very few adverse events. AR 0887.	Disputed in part. The cited statement refers to mifepristone for uses aside from termination of pregnancy. *See* AR 0887 & n.80. Not disputed that, in the context that "the pharmacology of mifepristone does not suggest any carryover effect after one-time administration," "data from many other studies reported in the medical literature using mifepristone for, e.g., fibroids, uterine myoma meningioma, psychiatric illnesses, and Cushing's

		disease, in much higher daily and lower daily doses for chronic use (months) have not raised any major safety issues." AR 0887. Disputed in that the fact is not material to this case.
14	In 2015-2016, the FDA "evaluated ... whether each Mifeprex REMS element remains necessary." JSF ¶ 26 & Ex. I, at 0680.	Not disputed.
15	In 2016, the FDA removed the Mifeprex REMS requirement that the drug sponsor (Danco) report serious adverse events except death, concluding it was "no longer warranted" given that "no new safety concerns have arisen in recent years, and that the known serious risks occur rarely." AR 0535 (2016); JSF Ex. C, at 0407.	Not disputed that FDA determined "ongoing reporting by certified healthcare providers to the Applicant of all of the specified adverse events is no longer warranted. It should be noted that the Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience reports." AR 0535. The REMS states "Danco Laboratories must report to FDA any death associated with Mifeprex whether or not considered drug-related, as soon as possible but no later than 15 calendars days from the initial receipt of the information by the applicant." JSF Ex. C at 0407. Disputed in that the fact is not material to this case.
16	The 2016 REMS Review for Mifeprex addressed none of the statutory benefit/risk factors	Disputed in part. The 2016 REMS Review evaluated whether a REMS "is necessary to ensure that the benefits of

	except that Mifeprex is "well-understood after more than 15 years of marketing" and "[s]erious adverse events are rare." JSF Ex. I, at 0681.	the drug outweigh the risks of the drug," pursuant to 21 U.S.C. § 355-1(a)(1). JSF Ex. I at 0680; *see also id.* at 0679, 0681, 0688-89, 0702, 0707. Not disputed that the cited quotes are accurate quotes for JSF Ex. I at 0681.
17	The 2016 REMS Review for Mifeprex did not list the 2013 REMS Review among the "Materials Informing Our Review." JSF Ex. I, at 0701.	Not disputed that the "Material Reviewed" list at JSF Ex. I at 0701 does not expressly contain the 2013 REMS Review. Disputed in that the fact is not material to this case.
18	Numerous laws and ethical standards require clinicians to prescribe only medications they are qualified to provide, and to obtain informed consent. Schreiber ¶¶58, 67, 76.	Not disputed that the practice of medicine is regulated by the states. Disputed in that the cited Declaration paragraphs provide no support for its assertions of requirements of "[n]umerous laws and ethical standards," Schreiber ¶¶ 58, 67, 76, and disputed in that the fact is not material to this case.
19	In an emergency, all clinicians can refer patients to the nearest Emergency Department, ensuring access to surgery, blood transfusions, and resuscitation. Schreiber ¶64.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.
20	All clinicians with prescriptive authority are qualified to understand Mifeprex's prescribing information. Schreiber ¶65.	Not disputed that clinicians with state-licensed prescribing authority are qualified to understand any prescribing information sufficiently to discern whether they are qualified to prescribe or administer a particular drug. Disputed otherwise, and disputed in that the fact is not material to this case.

21	Virtually all clinicians who care for pregnant patients and issue prescriptions are trained to diagnose and date an intrauterine pregnancy, and those who are not can obtain this information by ordering an ultrasound. Schreiber ¶¶59-63; JSF ¶67.	Not disputed insofar as: "Any provider who is not comfortable using patient medical history or a clinical examination to assess the duration and location of a pregnancy can obtain that information by ordering an ultrasound." JSF ¶ 67. Disputed because some clinicians care for pregnant women for medical issues unrelated to the pregnancy (*e.g.*, migraines, asthma) and would not necessarily be trained to diagnose and date an intrauterine pregnancy. Disputed in that the cited Declaration and Stipulation paragraphs provide no support as to abilities of "[v]irtually all clinicians who care for pregnant patients and issue prescriptions," Schreiber ¶¶ 59-63, JSF ¶ 67, and disputed in that the fact is not material to this case.
22	In removing language from the Mifeprex labeling suggesting patients take both drugs "at [their] provider's office," FDA relied on a study finding "no significant difference in either efficacy or safety" when patients took mifepristone at home. AR 0566 (2016).	Not disputed that language from the Mifeprex labeling requiring administration of Mifeprex at a provider's office was removed. Disputed that FDA relied on "a study;" FDA relied on several studies to support its decision. *See, e.g.*, AR 0565-68, 0575, 0588-90.
23	Concerns about "confidentiality" and "personal safety" do "not meet the criteria for requiring a REMS." JSF Ex. H, at 0356.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.

24	A Medication Guide provides risk-management information in patient-friendly language. Decl. of Peter Mathers, J.D., attached as Ex. B, at ¶12.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.
25	The Mifeprex Patient Agreement is "duplicative of information in the Medication Guide," "does not add to safe use conditions," and "is a burden for patients." JSF ¶41; AR 0437 (2016).	Disputed in part. Not disputed that the quoted view was expressed by certain FDA employees at a certain point, JSF ¶ 41; AR 0437, but CDER ultimately decided to retain the Patient Agreement. FDA also found the Patient Agreement to "foster[] active patient education and participation in this regimen." Defs.' CSMF ¶ 31 (quoting Defs.' Ex. 12 at 0224).
26	Evidence-based "off-label" use of drugs is common and widely accepted. Schreiber ¶80.	Not disputed that drugs are sometimes prescribed for off-label use. *See, e.g.*, 21 C.F.R. § 208.20(b)(8)(1). Disputed in that the fact is not material to this case.
27	From 2000-2016, evidence-based practice evolved such that Mifeprex's labeling (e.g., regarding dosage) no longer reflected the standard of care. Schreiber ¶80.	Not disputed that this statement reflects the clinician's experience. Not disputed to the extent that "[i]n 2015, Danco submitted an SNDA seeking approval to alter the Mifeprex indication, labeling, and REMS to reflect an updated, evidence-based prescription regimen." JSF ¶ 25. Disputed in that the fact is not material to this case.
28	The Patient Agreement does not reflect evolutions in evidence-based practice since 2016. Schreiber ¶¶79-80; Decl. of Jane Roe, M.D., attached as Ex. C, at ¶23.	Disputed. The Patient Agreement Form reflects the modifications approved in 2016, which are the most recent substantive modifications. *See, e.g.*, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-

		29_Patient_Agreement_Form.pdf. Moreover, the cited Declaration paragraphs discuss only the declarants' own experiences with the Patient Agreement, not any "evolutions in evidence-based practice since 2016." Also disputed in that the fact is not material to this case.
29	The Patient Agreement, which is not tailored to a patient's clinical circumstances, can confuse abortion patients and traumatize patients using Mifeprex for miscarriage management. Schreiber ¶¶76-82; Roe ¶¶23-24; AR 0437.	Not disputed that the Patient Agreement Form is the same for all patients, and not disputed as to the clinicians' representations of their own patients' experiences. Disputed otherwise in that FDA also found the Patient Agreement to "foster[] active patient education and participation in this regimen." Defs.' CSMF ¶ 31 (quoting Defs.' Ex. 12 at 0224), and disputed in that the fact is not material to this case.
30	The Mifeprex REMS removes the opportunity for additional counseling by pharmacists, such as regarding potential drug interactions. Decl. of Paul Lofholm, Pharm. D., attached as Ex. D, at ¶¶12, 16; Schreiber ¶50.	Not disputed that the REMS allows dispensing by certified health care providers only. JSF Ex. C at 0404-05. Disputed as to removal of "opportunity" for additional counseling by pharmacists because the REMS does not prohibit patients from seeking such additional counseling, JSF Ex. C, and disputed in that the fact is not material to this case.
31	FDA's Center for Drug Research and Evaluation houses the offices principally responsible for REMS decisions. Mathers ¶14.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.
32	It is extremely unusual for the FDA Commissioner to weigh in	Not disputed as to the attorney declarant's experience with FDA

	on a REMS decision, much less overrule the scientific review team. Mathers ¶¶15-16, 18.	Commissioner involvement in REMS decisions. Disputed that the Commissioner "overrule[d] the science review team" here, *see* JSF ¶¶ 40-41, and disputed in that the fact is not material to this case.
33	Abortion access is "very limited" in Hawaii and much of the United States. AR 540 (2016); Decl. of Diana Pearce, Ph.D., attached as Ex. E, at ¶¶5-6, 47.	Not disputed that "*some geographical areas* in the US have very limited availability of both the surgical and medical options or even one option for early pregnancy termination." AR 0540 (emphasis added). Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
34	In more than half the states, at least 20% of reproductive-age women live more than 50 miles from the nearest abortion clinic. Pearce ¶47.	Not disputed that one of the cited pages of the Lancelet article (page e497) states: "The median distance to the nearest clinic providing abortion services in 2014 was 15–29 miles 24–47 km) in 16 (32%) states and 30–89 miles (48–143 km) in eight (16%) states. At least half of all women in three (6%) states, including Wyoming (168.49 miles [271.16 km]), North Dakota (151.58 miles [243.94 km]), and South Dakota (92.06 miles [148.16 km]), would have had to travel more than 90 miles (145 km) to reach the nearest clinic." Not disputed that the other articles cited in Pearce ¶ 47, n.61 discuss the distance women in Louisiana, Arizona, and Alabama traveled to reach an abortion clinic in the years studied.

35	A recent study characterized 27 major cities as "abortion deserts" with no publicly advertised provider within 100 miles. Pearce ¶¶6, 26.	Not disputed as to the cited study's characterization. Disputed in that Defendants are without information to otherwise dispute or not dispute, and disputed in that the fact is not material to this case.
36	But for the REMS, more clinicians would provide medication abortion. Decl. of Joey Banks, M.D., attached as Ex. F, at ¶¶15-16, 23; Decl. of Graham Chelius, M.D., attached as Ex. G, at ¶¶8, 16, 28, 38, 42; Decl. of Jared Garrison-Jakel, M.D., attached as Ex. H, at ¶¶9-10, 14; Decl. of Charisse Loder, M.D., attached as Ex. I, at ¶25; Roe ¶25; Schreiber ¶83; Decl. of Eleanor Bimla Schwarz, M.D., attached as Ex. J, at ¶¶4, 15-16.	Not disputed as to clinicians' representations of their own intentions or desires.
37	Recent research shows that of OB-GYNs who had not provided Mifeprex in the previous year, nearly 30% would have done so if they could write a prescription. Schreiber ¶83.	Not disputed that referenced article relied on "[a] national sample of American College of Obstetricians and Gynecologists Fellows and Junior Fellows who were part of the Collaborative Ambulatory Research Network," and further stated, "[t]he most common reasons for not providing medication abortion were personal beliefs (34%) and practice restrictions (19%). Among those not providing medication abortion, 28% said they would if they could write a prescription for mifepristone." Grossman, *et al.*, abstract.

		[https://www.ncbi.nlm.nih.gov/pubmed/30741798]. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
38	"Consistent with data from other sources," a study found "difficulty obtaining supplies" among the three "greatest barriers to providing an abortion." JSF Ex. H, at 11.	Not disputed that the cited study stated: "Relative to providers, the greatest barriers to providing an abortion reported by non-providers were lack of skills, concerns about liability, and difficulty obtaining supplies. Although these data were limited to RHP trainees, data are consistent with data from other sources and provides additional insight into what facilitates abortion care and barriers." AR 0354.
39	Many clinicians who would be able to write a prescription for Mifeprex find it difficult or impossible to dispense Mifeprex onsite. Schreiber ¶83; Chelius ¶¶8, 30-31; Garrison-Jakel ¶¶9-10, 14; Roe ¶¶4, 9-22, 25; Loder ¶14; Schwarz ¶¶11-13, 16; Banks ¶¶15-16.	Not disputed as to the clinicians' representations of their own experience. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
40	Securing approval to stock Mifeprex, and developing protocols to store, dispense, and bill for it onsite, can require substantial time and jeopardize clinicians' reputations and relationships. Chelius ¶¶30-31, 39-40; Loder ¶¶5-14, 20, 28; Roe ¶¶9-22; Schwarz ¶¶10-12.	Not disputed as to the clinicians' representations of their own experience. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.

41	Plaintiff Chelius does not provide Mifeprex because attempting to dispense it onsite would threaten his reputation and relationships, but would be able to write a pharmacy prescription. Chelius ¶¶8, 28-31.	Not disputed that that is Dr. Chelius's asserted reason. Chelius ¶¶ 8, 28-31. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
42	Plaintiff California Academy of Family Physicians member Garrison-Jakel does not provide Mifeprex because a colleague opposes stocking it at their clinic, but would be able to write a pharmacy prescription. Garrison-Jakel ¶10.	Not disputed that that is Dr. Garrison-Jakel's asserted reason. Garrison-Jakel ¶ 10. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
43	Because the responsibilities for purchasing, storing, dispensing, and billing are often divided across staff, the REMS injects many more people into abortion care, posing confidentiality risks. Chelius ¶¶35-38; Roe ¶21.	Disputed. Removing the REMS would involve more people, such as pharmacists, pharmacist technicians, and clerks. *See, e.g.*, PCSF ¶ 30, Pls.' MSJ at 30. Also disputed in that the fact is not material to this case.
44	These confidentiality concerns are an additional reason Plaintiff Chelius does not provide Mifeprex in his town of 2,000 on Kaua'i. Chelius ¶¶35-38.	Not disputed that that is Dr. Chelius's asserted reason. Chelius ¶¶ 35-38. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
45	The Prescriber Registration deters Mifeprex provision because clinicians fear anti-abortion violence if their registrations became public. Schreiber ¶¶68-70; Chelius ¶¶32-34; Banks ¶10, 16; Risk Mitigation Review for Korlym, attached as Ex. K, at 0301.	Not disputed as to clinicians' representations of their own experience. However, the REMS requires manufacturers to ensure that distributors who distribute Mifeprex put processes in place to maintain a confidential distribution system. JSF Ex. C at 0406.

46	Plaintiff Society of Family Planning ("SFP") members have spent up to five years trying to navigate the approvals and protocols necessary to stock Mifeprex in their large medical institutions. Roe ¶¶9-22; Loder ¶¶5-20, 28; Schwarz ¶¶10-12, 15.	Not disputed as to clinicians' representations of their own experience.
47	The REMS categorically bars Plaintiff Pharmacists Planning Services Inc. members from dispensing Mifeprex. Lofholm ¶¶8, 17.	Disputed. The REMS does not "bar" particular providers but instead permits dispensing only by certified healthcare providers who prescribe and "in clinics, medical offices and hospitals by or under the supervision of a certified prescriber." JSF Ex. C at 0404-06.
48	Most abortion patients are low-income and have at least one child. Pearce ¶¶38-39	Accuracy of fact not disputed, but disputed in that the fact is not material to this case because is true for surgical and medication abortions.
49	Most single mothers, particularly single mothers of color, have income inadequate to meet their families' needs. Pearce ¶17.	Not disputed as to the stated results of Dr. Pearce's cited studies in Pennsylvania and California. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
50	When a provider must refer a low-income patient elsewhere for a medication abortion, the costs and burdens associated with abortion are compounded and can be insurmountable. Pearce ¶¶20-21, 23-25, 35, 46, 50-52.	Not disputed that one of the studies relied on by Dr. Pearce, *see* Pearce ¶ 46, 50-51, stated: "Standardized measurements of travel, including burdens associated with travel and more nuanced considerations of travel costs, should be implemented in order to facilitate comparison across studies. More research is needed to explore and accurately capture different dimensions

		of the burden of travel for abortion services on women's lives." *See* https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0209991&type=printable. Not disputed as to the results of the cited studies for Pennsylvania, California, and Arizona. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
51	The burdens of abortion travel typically include transportation, childcare, meals, and lost wages. Pearce ¶¶23-32, 34-38.	Not disputed as to the stated results of the cited studies. Disputed in that the fact is not material to this case because would be true for both surgical and medication abortions; and that Defendants are without sufficient information to dispute or not dispute it.
52	Few low-wage workers have paid time off. Pearce ¶36.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.
53	Childcare is particularly expensive outside regular hours. Pearce ¶38.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.
54	Traveling for an abortion may necessitate overnight lodging to accommodate early appointments, multi-day procedures, or cheaper flights. Pearce ¶32.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case because is true for both surgical and medication abortions.
55	For women living on Kauaʻi, Hawaiʻi, Lanaʻi, Molokaʻi, or Niʻihau, obtaining an abortion generally means a flight to Oʻahu	Accuracy of fact not disputed, but disputed in that the fact is not material to this case because is true for both surgical and medication abortions.

	plus ground transportation. Pearce ¶¶5, 23; Chelius ¶¶11-12.	
56	Even for the minority of patients able to use insurance for abortion and related travel, insurance will not pay for childcare, meals, or lost wages. Pearce ¶34.	Not disputed that "the same 2014 study found that only one in four patients with private insurance had their abortion covered by insurance." Pearce ¶ 34. Disputed in that the fact is not material to this case because would be true for both surgical and medication abortions; and that Defendants are without sufficient information to dispute or not dispute it.
57	To make arrangements and secure funds for travel, women often forego essential needs, like groceries or rent, or borrow at high rates. Pearce ¶¶41-43.	Not disputed that unexpected health care costs can have negative consequences. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
58	To make arrangements and secure funds for travel, some women must disclose their pregnancy and abortion, such as to an employer to explain her absence, or to an abusive partner. Pearce ¶¶44-45.	Not disputed that unexpected health care costs can have negative consequences. Disputed in that the fact is not material to this case because would be true for both surgical and medication abortions; and that Defendants are without sufficient information to dispute or not dispute it.
59	The travel and logistics caused by the REMS can impinge a woman's privacy, jeopardize her employment, put her at risk for violence, and destabilize her	Disputed in that the statements do not demonstrate or support how the REMS is the cause, rather than other factors. Disputed in that the fact is not material to this case; and that Defendants are

	family economically. Pearce ¶¶23, 46, 51.	without sufficient information to dispute or not dispute it.
60	The travel and logistics caused by the REMS disproportionally injure low- income and rural women and women of color. Pearce ¶¶6, 17, 19, 22, 25, 47, 52; Chelius ¶¶11-12, 18; Garrison-Jakel ¶¶6-8, 11; Roe ¶¶7-8, 12; Banks ¶¶17-21.	Disputed in that the statements do not demonstrate or support how the REMS is the cause, rather than other factors. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
61	SFP's 2016 letter to the FDA explained that fewer patients can access medication abortion because of the REMS, and that these burdens hit rural and low-income communities hardest. JSF Ex. F, at 1255.	Not disputed that is an accurate description of SFP's 2016 letter to FDA, which letter speaks for itself. JSF Ex. F at 1255. Disputed in that the fact is not material to this case; and that Defendants are without sufficient information to dispute or not dispute it.
62	An extensive body of research spanning multiple states and decades finds that when women must travel longer distances to obtain an abortion, even by only 10-12 miles, some are prevented from doing so. Pearce ¶¶46-51.	Not disputed that the 10-12-mile figure was based on the cited studies in Georgia and Washington. Pearce ¶¶ 46-51. Disputed in that the fact is not material to this case because would be true for both surgical and medication abortions; and that Defendants are without sufficient information to dispute or not dispute it.
63	A 2017 study found that when the distance to the nearest abortion facility increased by more than 100 miles, abortions decreased by half. Pearce ¶48.	Not disputed that the study "evaluated the impact of a law that closed 24 of 41 abortion clinics in Texas." Pearce ¶ 48. Disputed in that the fact is not material to this case because would be true for both surgical and medication abortions;

		and that Defendants are without sufficient information to dispute or not dispute it.
64	Plaintiffs and their members have had patients carry unwanted pregnancies to term because the REMS prevented them from writing a prescription for Mifeprex. Chelius ¶17; Garrison-Jakel ¶13; Roe ¶8.	Disputed in that the declarations do not explain or support how the REMS, rather than other factors, was cause of clinicians' experience.
65	By reducing the availability of Mifeprex and increasing the costs and burdens to obtain this care, the REMS delays abortions. Pearce ¶¶8, 25, 33, 35, 46, 49, 52; Chelius ¶¶10, 13-16; Roe ¶¶8, 12; Loder ¶¶22-24; Garrison-Jakel ¶¶11-12; Banks ¶21; Schwarz ¶14.	Disputed in that the declarations do not explain or support how the REMS, rather than other factors, is the cause.
66	Delay means a patient must bear the risks and burdens of pregnancy longer. Schreiber ¶84; Chelius ¶13.	Accuracy of fact not disputed to the extent that "delay" refers to delay in obtaining an abortion, but disputed in that the fact is not material to this case.
67	While abortion is safe, the associated risks increase as pregnancy advances. Schreiber ¶84.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.
68	Delays may mean medication abortion is no longer available, or necessitate a two-day abortion procedure. Chelius ¶¶10, 14-15; Schwarz ¶14; Pearce ¶49.	Accuracy of fact not disputed to the extent that "delay" refers to delay in obtaining an abortion and "two-day abortion procedure" refers to a second trimester abortion, but disputed in that the fact is not material to this case.
69	The 2012 Korlym REMS Review considered that a REMS can "reduce[] access" and cause	Not disputed that the 2012 Korlym REMS Review stated such as to the Korlym REMS only. Pls.' Ex. K at

	"treatment delays." Ex. K, at 0303-04.	0303-04. Disputed in that the fact is not material to this case.
70	FDA has never analyzed how the Mifeprex REMS burdens access and whether those burdens are undue. JSF Exs. H & I.	Disputed. FDA evaluated burdens. *See, e.g.*, AR at 0571, 0675, 0589, 0375, 0377.
71	FDA approved approximately 1,000 new drug applications ("NDAs") in the 15 years preceding the enactment of the 2007 REMS statute, and subjected only 7, including Mifeprex, to special restrictions under Subpart H. Mathers ¶19.	Not disputed that the cited GAO report entitled "Approval and Oversight of the Drug Mifeprex" states that 7 drugs had NDAs that were approved under Subpart H, and that the cited GAO report entitled "Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts" calculated that as of September 2005, 961 of 1,264 NDAs submitted from January 1, 1993, through December 31, 2004, had been approved. Disputed in that the fact is not material to this case.
72	Korlym®, mifepristone approved for treatment of Cushing's Syndrome, has no REMS and is available through a specialty mail-order pharmacy pursuant to a voluntary restricted distribution system. JSF ¶¶62, 65; Schreiber ¶36. 73.	Not disputed.
73	In evaluating the Korlym NDA, FDA stated that the "challenge of this application is because of the more controversial use of this active ingredient for medical termination of pregnancy." AR 0310 (2012)	Not disputed.
74	FDA stated that "appropriate labeling and use of Korlym by specialists well- versed in the care	Not disputed as to accuracy of the quote. Disputed insofar as a variety of other factors were also considered in

	of patients with Cushing's syndrome should allow safe and effective use," without a REMS. AR 0327; accord 0325 (2012).	determination not to impose REMS. AR 0301-03.
75	FDA's Korlym REMS Review analyzed each of the statutory benefit/risk factors before determining that a REMS was not necessary. Ex. K, at 0296-0301.	Not disputed.
76	FDA's Korlym REMS Review considered that misoprostol's "risk of termination of pregnancy" "is managed through labeling (Contraindication, Boxed Warning)," without a REMS. Ex. K, at 0300.	Not disputed that for Korlym, pregnancy loss is a "risk" to be avoided; not an intended use. AR 0300; *see also* AR 0328 ("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.").
77	Korlym is taken for "years/decades," "in higher doses, in a chronic, daily fashion … [and] the rate of adverse events with Mifeprex is much lower." Ex. K, at 0297; AR 0537 (2016).	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.
78	"Korlym [is] distributed directly to patients … packaged in bottles of 28 and 280, making diversion and pilfering presumably easier relative to the Mifeprex packaging." Ex. K, at 0299.	Not disputed that the quote is accurate from the Korlym review memo, which also notes, "Similar to Korlym, there is potential for Mifeprex to be pilfered or diverted from a distribution facility, during shipping, or at the place of dispensing." AR 0299.
79	Misoprostol acts as an abortifacient although labeled for ulcer treatment. Schreiber ¶11.	Not disputed that misoprostol has abortifacient properties and that "Cytotec (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, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer." *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019268s041lbl.pdf
80	The Mifeprex-misoprostol regimen is safer and more effective than misoprostol alone and thus the standard of care for both early abortion and miscarriage management. Schreiber ¶¶11, 15-16, 39-42.	Disputed in part, regarding the use of Mifeprex for "miscarriage management." Not disputed that Mifeprex is indicated in a regimen with misoprostol for the medical termination of intrauterine pregnancy through 70 days gestation. AR 0383.
81	Patients using the Mifeprex-misoprostol regimen typically expel the pregnancy 2-24 hours after taking misoprostol. JSF Ex. A, at 0385.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.
82	The extremely rare complications of heavy bleeding or infection would most likely occur after the patient has taken the misoprostol, 24-48 hours after she took Mifeprex. JSF Ex. A, at 0385-86; Schreiber ¶¶40, 50-51.	Not disputed that the Mifeprex labeling instructs patients to take misoprostol 24 to 48 hours after taking Mifeprex, AR 0385, and that the remainder of the statement is an accurate representation of Dr. Schreiber's patients' experiences.
83	Misoprostol has no REMS and is available at virtually any retail pharmacy. Schreiber ¶38.	Disputed in part. Not disputed as to lack of REMS; disputed as to availability at "virtually any retail pharmacy," as to which no party has complete information.
84	Misoprostol's labeling warns that "[p]atients must be advised of the abortifacient property and warned not to give the drug to others." Schreiber ¶43.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.

85	Misoprostol's risks include "severe genital bleeding" and "fetal and maternal death." Schreiber ¶43 (quoting labeling).	Not disputed that the quoted adverse events have been reported with the obstetrical use of Cytotec (the brand name for misoprostol).
86	Warfarin, an anticoagulant (blood thinner) often taken on a long-term basis to treat common clotting conditions, does not have a REMS and is available at pharmacies. Schreiber ¶37.	Not disputed.
87	Warfarin's labeling carries a black box warning of "major or fatal bleeding," ranging from 0.6% to 2.7%. for patients with certain conditions. Schreiber ¶37.	Not disputed as to Warfarin's boxed warning. Disputed in part because the cited page of the Warfarin label states: "The incidence of major bleeding in these [five prospective, randomized, controlled clinical] trials ranged from 0.6% to 2.7%."
88	Of the 15 drugs FDA requires patients to obtain only in certified healthcare settings, Mifeprex and its generic are the only ones for which FDA does not also regulate where the patient takes it. For all others, the dosage form (e.g., intravenous) necessitates that it be administered in certain settings, or the labeling states that it can be safely administered only in certain settings (e.g., so the clinician can monitor for immediate reactions such as "life-threatening respiratory depression," or to prevent patient abuse). JSF ¶60; Schreiber ¶¶29-31.	Accuracy of fact not disputed, but disputed in that the fact is not material to this case.

Defendants also contend that the following additional material facts are relevant to the Court's determination:

Defendants' Statement of Additional Material Facts in Opposition

#	Additional Fact	Source
1	As part of the 2016 REMS Review, FDA 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); JSF Ex. I at 0681; JSF ¶¶ 50, 57; *see generally* JSF Exs. H, I.
2	Without the restricted dispensing requirement, patients might not receive proper counseling at the time of dispensing about the serious complications associated with Mifeprex or what to do if they experience such complications.	JSF Ex. H at 0356.
3	Without the restricted dispensing requirement, patients might delay picking up their Mifeprex prescription and initiating an abortion, resulting in increased risk.	JSF Ex. H at 0356.
4	Without the restricted dispensing requirement, patients who have a hard time finding a pharmacy that stocks Mifeprex may experience a delay with potential complications.	JSF Ex. H at 0356.
5	In submitting the supplemental new drug application ("sNDA") that led to FDA's 2016 review of the Mifeprex REMS, the	Defs.' Ex. 20 at 0414-15, 0435

	sponsor proposed only limited modifications to the existing REMS.	
6	FDA does not approve modifications to a drug's REMS absent an adequate rationale for the changes, including data to support the proposed changes.	REMS: Modifications and Revisions (Jul. 2019), Defs.' Ex. 39 at 12.
7	The skills contained in the Prescriber Agreement Form are necessary to ensure that prescribers of Mifeprex are "very familiar with managing early pregnancy."	Defs.' Ex. 12 at 0227
8	FDA determined that the Prescriber Agreement Form is necessary to ensure that 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.	Defs.' Ex. 22 at 0576.
9	During the 2016 REMS review, the FDA Commissioner provided input on a single ETASU—the Patient Agreement Form.	Compl. Ex. D at 1.
10	The authority the Agency exercises when imposing REMS requirements is authority that the Secretary of HHS has delegated to the Commissioner.	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.
11	FDA's 2019 REMS Guidance explains the Agency is required look at each drug independently, assessing each drug's risks in comparison to that same drug's benefits.	Defs.' Ex. 35 at 4.
12	Korlym and Mifeprex share the same active ingredient, but they have very different approved indications and patient populations.	Defs.' Ex. 14, 15, 16.
13	FDA evaluates an active ingredient based on the risk benefit profile for the intended population.	Defs.' Ex. 15 at 0301.
14	Korlym is indicated "to control hyperglycemia secondary to	Defs.' Ex. 15 at 0271.

	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."	
15	Cushing's syndrome is an extremely rare and sometimes fatal disease.	Defs.' Ex. 15 at 0296-97.
16	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.
17	The probability that a Cushing's patient will become pregnant while on Korlym is very low.	Defs.' Ex. 15 at 0304.
18	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, 0271.
19	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).
20	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."	Cytotec, misoprostol tablets, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019268s051lbl.pdf
21	Warfarin is a very old and widely prescribed anticoagulant.	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

Dated: January 10, 2020

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CERTIFICATION

I certify, using the word count feature of Microsoft Word, that the above additional facts consist of 703 words, below the 2,500 word limit requested by the parties (Dkt. No. 79) (granted in part by Dkt. No. 82).

/s/ Roger Gural
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Defendants' Exhibit 39

Risk Evaluation and Mitigation Strategies: Modifications and Revisions

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2019
Drug Safety

Revision 1

Risk Evaluation and Mitigation Strategies: Modifications and Revisions

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2019
Drug Safety

Revision 1

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Contains Nonbinding Recommendations

Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information on how the FDA defines the types of changes to approved risk evaluation and mitigation strategies (REMS), how application holders[2] should submit changes to an approved REMS,[3] and how the FDA will process submissions from application holders for changes to REMS. Specifically, this guidance provides information, as described in section 505-1(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), on what types of changes to REMS will be considered ***modifications*** of the REMS and what types of changes will be considered ***revisions*** of the REMS (changes that may be implemented following notification to the FDA).[4] This guidance is issued pursuant to section 505-1(h)(2)(A)(ii), (iii), and (iv) of the FD&C Act and section 1132(c) of Public Law 112-144.

[1] This guidance has been prepared by the Office of New Drugs, the Office of Surveillance and Epidemiology, and the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] Under section 505-1(b)(7) of the Federal Food, Drug, and Cosmetic Act, the term *responsible person* means "the person submitting a covered application or the holder of the approved such application." For ease of reference, this guidance refers to a responsible person as an *application holder*.

[3] The REMS is the enforceable document that describes the elements that an application holder is required to implement to mitigate a specific, serious risk listed in the labeling of the drug. All proposed materials that are included as part of the REMS (e.g., communication and educational materials, Medication Guide, patient package insert, enrollment forms, prescriber and patient agreements) are also approved, and are appended to the REMS document. This guidance refers to these materials as *REMS materials*.

[4] See 21 U.S.C. 355-1(h)(2)(A) and P.L. 112-144, §1132(c).

This guidance applies to all types of REMS, including REMS that are part of a shared system (SS REMS).[5,6]

This guidance does not address additional submission procedures that may apply to application holders proposing changes to REMS that are part of a shared system and that use a drug master file (DMF) for their REMS submissions.[7]

This guidance is being issued consistent with the FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the Agency's current thinking on changes to REMS. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

II. BACKGROUND

A REMS is a required risk management plan that uses tools beyond the prescribing information (the package insert) to ensure that the benefits of certain drugs outweigh their risks.[8] If the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks, the FDA is authorized to require a REMS for such drugs under section 505-1 of the FD&C Act.[9] Section 505-1(g) and (h) includes provisions regarding the assessment and modification of an approved REMS.

An application holder may propose a REMS modification at any time. In addition, when the FDA determines that a modification of a REMS is necessary to ensure that the benefits of a drug outweigh its risks or to minimize the burden on the health care delivery system of complying with the REMS, the FDA has the authority to require that the application holder submit a proposed modification to a REMS under section 505-1(g) of the FD&C Act.

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[5] For the purposes of this guidance, a *shared system* REMS (SS REMS) is a program that encompasses multiple prescription drugs and is developed and jointly implemented by two or more application holders. An SS REMS includes a single, shared system REMS as defined in section 505-1(i)(1)(B) of the FD&C Act.

[6] See the draft guidance for industry *Development of a Shared System REMS* (June 2018). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] For submission procedures for changes to SS REMS that use a DMF for their submissions, see the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions* (November 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[8] For the purposes of this guidance, unless otherwise specified, references to *drugs* include drugs approved under the FD&C Act and biological products licensed under the Public Health Service Act (PHS Act), other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

[9] Section 505-1 applies to applications for prescription drugs submitted under FD&C Act subsections 505(b) (i.e., new drug applications) or (j) (i.e., abbreviated new drug applications), and applications under section 351 of the PHS Act (i.e., biologics license applications).

The Food and Drug Administration Safety and Innovation Act (FDASIA) amended the REMS modification provisions under section 505-1(g) and (h) of the FD&C Act. Section 505-1(h), as amended by FDASIA, requires the FDA to review and act on proposed *minor modifications*, as defined in guidance, within 60 days.[10] It also requires the FDA to establish, through guidance, that *certain modifications* can be implemented following notification to the FDA.[11] In addition, section 505-1(h) requires the FDA to review and act on REMS modifications to conform the strategy to approved safety labeling changes, or to a safety labeling change that the FDA has directed the application holder make pursuant to section 505(o)(4) of the FD&C Act, within 60 days.[12] Finally, section 505-1(g)(4)(A) of the FD&C Act as amended by FDASIA specifies that proposed REMS modifications no longer require submission of a REMS assessment; instead, proposed modifications must include an adequate rationale for the proposed changes.

Existing FDA regulations describe how to make changes to approved applications, and include a mechanism for rapid implementation of certain changes.[13] Some changes must be submitted as a prior approval supplement (PAS) and approved before they are implemented. Changes-being-effected (CBE) supplements may be implemented at the time they are submitted or 30 days following submission.[14] If a supplement was inappropriately submitted as a CBE, the FDA will notify the application holder that the proposed change(s) require FDA approval before implementation. A description of how these existing submission requirements apply to proposed REMS changes is provided below in greater detail.

III. POLICY

Changes to REMS will be categorized as REMS revisions, minor REMS modifications, or major REMS modifications, based on the degree of their potential effect on (1) the information provided in the REMS related to the serious risk(s) associated with the drug; (2) the safe use of the drug; and/or (3) the actions that the application holder, patients, health care providers, and other stakeholders must take to comply with the REMS.

---

[10] See section 505-1(h)(2)(A)(ii) of the FD&C Act. Section 1132(c) of FDASIA also provides that the FDA "shall issue guidance that, for purposes of section 505-1(h)(2)(A) of the [FD&C Act], describes the types of modifications to approved risk evaluation and mitigation strategies that shall be considered to be minor modifications of such strategies."

[11] See section 505-1(h)(2)(A)(iv) of the FD&C Act. The FDA interprets *certain modifications* that can be implemented upon notification to the FDA to be changes to a REMS that are editorial in nature or appropriate for submission in an annual report, and therefore calls these REMS changes *revisions* to differentiate these changes from modifications that require the submission of a supplement and the FDA review and action.

[12] See section 505-1(h)(2)(A)(iii) of the FD&C Act.

[13] See 21 CFR 314.70 and 601.12.

[14] PAS-proposed changes must be approved by the FDA before implementation (21 CFR 314.70(b) and 21 CFR 601.12(b)(3) and (f)(1)). CBE supplements contain changes that may be implemented by the application holder either immediately upon FDA receipt of the supplement (CBE-0 supplements) (21 CFR 314.70(c)(6) and 601.12(c)(5) and (f)(2)(ii)) or 30 days after FDA receipt of the supplement (CBE-30 supplements) (21 CFR 314.70(c) and 601.12(c)(3)).

Tables 1 through 4 provide examples of REMS revisions and minor and major REMS modifications. These tables are intended to be a representative, rather than comprehensive, list of examples.

A. REMS Revisions

REMS revisions are defined as editorial changes that *do not affect*:

- The information contained in the REMS document and/or REMS materials about the serious risk or safe use of the drug
- The actions application holders, patients, health care providers, or other stakeholders must take to comply with the REMS, or the REMS materials that support those actions

Examples of REMS revisions are provided in Table 1.

Table 1. REMS Revisions (Submitted as REMS Revisions and Summarized in the Annual Report)[15]

Examples[a]
• Changes in the application holder name or address to reflect transfer of application ownership[b]
• Updates to the application holder's contact information (e.g., mailing address, telephone number, fax number, and/or email address)
• Editorial changes, such as: – Changes in International Classification of Diseases code(s) in the REMS materials or on the REMS website – Changes to the application holder's internal tracking information (e.g., tracking numbers) on REMS forms – Changing the application holder's signatory for a Dear Health Care Provider Letter that is part of the REMS materials – Changing a trademark symbol, designated by ™, to the registered trademark symbol, designated by ® – Changes to the approved package count configuration that result in changes to the REMS materials (e.g., a change in the national drug code number(s))

continued

[15] See section IV., Submission Procedures.

Table 1, continued

Examples[a]
• Correction of grammatical, formatting, and/or typographical errors, for example: *"[DRUG] ~~are~~ <u>is</u> associated with the potential ~~risk~~ <u>risks</u> of seizure and hepatotoxicity."* *"Health care ~~prviders~~ <u>providers</u> who prescribe [DRUG] must be ~~specally~~ <u>specially</u> certified."*
• The following changes to a Medication Guide that is an element of a REMS:[c] – Changes in the application holder's name and/or place of business[d] – Insertions of the date of the most recent revision of the Medication Guide[e] – Addition of the side effects statement and toll-free number for reporting adverse events to a Medication Guide[f]

[a] The types of REMS changes in *italic font* are provided for illustrative proposes. Additions are noted by <u>underline</u> and deletions are noted by ~~strikethrough~~.

[b] Application holders are responsible for reporting a transfer of ownership in accordance with Federal regulations. The FDA must be notified in writing by the new and former application holders at the time of transfer in ownership of a new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA) (21 CFR 314.72; 21 CFR 601.12(f)(1)).

[c] See 21 CFR 314.70(b)(2)(v)(B) for NDAs and 21 CFR 601.12(f)(3)(C) for BLAs.

[d] See 21 CFR 208.20(b)(8)(iii).

[e] See 21 CFR 208.20(b)(8)(iv).

[f] See the guidance for industry *Medication Guides — Adding a Toll-Free Number for Reporting Adverse Events* (June 2009). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

B. REMS Modifications

Proposed REMS modifications are divided into two categories: minor modifications and major modifications.

1. Minor REMS Modifications

Minor REMS modifications are defined as changes that have *a limited effect* on:

- The information contained in the REMS document and/or REMS materials about the serious risk or safe use of the drug

- The actions application holders, patients, health care providers, or other stakeholders must take to comply with the REMS, or on the REMS materials that support those actions

These should be submitted as a CBE-30 supplement (see section IV., Submission Procedures). Examples of minor REMS modifications are provided in Table 2.

Table 2. Minor REMS Modifications (Submitted as CBE-30 Supplements[16])

Type of Change	Examples
Minor modifications that have a *limited effect* on information contained in the REMS about the serious risk or safe use of the drug	• Addition of an approved new strength or dosage regimen of the drug[a] • Removal of a strength or dosage form of the drug (other than from the Medication Guide) because either FDA approval has been withdrawn and documented by publication of a *Federal Register* notice for the strength/dosage form, or the FDA has determined that the strength/dosage form was withdrawn from sale for reasons of safety or effectiveness • Addition of an authorized generic • Adding, removing, or changing information about another drug that is mentioned in the REMS document and/or materials, but is not the drug for which the REMS was required – Adding a new, recently approved drug to a class of drugs already mentioned in the REMS materials as having the potential to cause drug-drug interactions • Adding information previously reviewed and approved for one application that is part of an SS REMS to the REMS document and/or REMS materials for the other applications in the SS REMS – Adding a new, recently approved drug in a class to the REMS document and/or REMS materials for the other applications in the SS REMS – Adding new information about an existing drug in a class to the REMS document and/or REMS materials for the other applications in the SS REMS • Changes to graphics, including changes to the existing manufacturer's logo or the logo for the REMS program

continued

[16] See section IV., Submission Procedures.

Table 2, continued

Type of Change	Examples
Minor modifications that have a *limited effect* on the actions application holders, patients, health care providers, and other stakeholders must take to comply with the REMS	• Adding a professional society to the list of required recipients of a Dear Health Care Provider Letter required in the REMS materials • Converting an existing prescriber enrollment form into another format to allow for online registration, in addition to paper enrollment via email or fax, without altering the prescriber certification requirements • Creating or converting an existing health care facility enrollment form to allow *closed* (i.e., self-contained) health care systems to enroll • Changing an existing health care provider or patient enrollment form to collect additional demographic information • Changes to the hours of operation for the REMS call center • Limited changes to the REMS website to improve functionality (ease of use) for stakeholders • Limited changes to the REMS website to clarify current processes required of stakeholders (e.g., changes to clarify how health care providers should navigate the website to complete enrollment in the REMS) • Adding approved REMS materials (new or modified) to the REMS website • Changing the timetable for submission of assessment for REMS involving multiple drugs in the same class and owned by the same application holder to synchronize the assessment due date(s) • Re-ordering the risk information in the REMS materials

[a] Proposals for a new dose regimen or strength of a drug are submitted as supplemental efficacy or chemistry, manufacturing, and controls (CMC) applications. Proposed REMS modifications submitted or required as part of an efficacy or CMC supplement will be reviewed and acted on as part of that supplement, and not according to the time frames described above for REMS revisions, minor modifications, or major modifications. See section V.F., REMS Modifications Included in Other Submissions.

2. Major REMS Modifications

Major REMS modifications are defined as changes that have *a substantial effect* on:

- The information contained in the REMS document and/or REMS materials about the serious risk or safe use of the drug

- The actions application holders, patients, health care providers, or other stakeholders must take to comply with the REMS, or the REMS materials that support those actions

Major REMS modifications include changes to provide new information about the serious risk(s) or safe use of the drug. In addition, modifications to the strategy due to approved safety labeling changes, or to a safety labeling change that the FDA has directed the application holder to make pursuant to section 505(o)(4) of the FD&C Act, are considered major REMS modifications. The FDA interprets REMS modifications that *conform to* safety labeling changes in section 505-1(h)(2)(A)(iii) of the FD&C Act to refer to modifications that transfer the newly approved labeling language into the existing REMS and/or REMS materials. Overall design, programmatic, and/or implementation changes to the REMS that result from approved (or ordered) safety labeling changes are *not considered conforming* REMS modifications.

Examples of major REMS modifications are provided in Tables 3 and 4. Major REMS modifications should be submitted as a PAS (see section IV., Submission Procedures).

Table 3. Major REMS Modifications (Submitted as a PAS[17])

Type of Change	Examples
Major modifications that have a *substantial effect* on information contained in the REMS about the serious risk or safe use of the drug	• Addition, removal, or change to a REMS goal • Addition of new information about the serious risks associated with the drug • Addition of a new indication for use that may alter the serious risks (in relation to benefits) of the drug for the new patient population[a] • Addition of new information about drug administration that affects patient safety • Changing the type, frequency, and/or timing of patient laboratory testing required as part of the documentation of safe-use conditions • Any change to a Medication Guide that is an element of a REMS and for which FDA approval of the change is required[b]

continued

[17] See section IV., Submission Procedures.

Table 3, continued

Type of Change	Examples
Major modifications that have a *substantial effect* on the actions applications holders, patients, health care providers, and other stakeholders must take to comply with the REMS	• Removing or adding an element of the REMS • Substantially modifying an existing REMS element, including: – Changes to the timetable for submission of assessments of the REMS that alter the frequency and/or number of the assessments – Changes to an ETASU[c] that modify the verification process required for the drug to be dispensed to patients – Adding a new letter to health professional societies to the REMS materials to describe new or clarified information about a serious risk – Adding/removing the REMS website from the communication plan or an ETASU • Substantial changes to a REMS tool, including: – Changing the prescriber enrollment form to add/remove an attestation that the prescriber understands the serious risk(s) of the drug – Extensive changes to a patient brochure to better educate patients about the serious risk(s) of the drug – Adding or removing a prescriber educational tool, such as a slide deck or safety information brochure • Modification that proposes releasing the REMS requirement • Changing a REMS for an individual product to an SS REMS[d]

[a] See section V.F., REMS Modifications Included in Other Submissions.

[b] See 21 CFR 314.70(b)(2)(v)(B) and 601.12(f)(1). For a Medication Guide that is an element of a REMS, if the changes are required under section 505(o)(4) of the FD&C Act, the changes should be submitted in accordance with the procedures described in the guidance for industry *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* (July 2013).

[c] ETASU = elements to assure safe use

[d] See the draft guidance for industry *Development of a Shared System REMS* (June 2018) for additional policies and procedures for modifying the REMS for an individual product to an SS REMS. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Table 4. REMS Modifications Due to Safety Labeling Changes (Type of Major Modification, Submitted as a PAS[18])

Type of Change	Examples
Changes that *are considered conforming* (i.e., modifications that transfer the newly approved labeling language into the existing REMS and/or REMS materials (60-day review))	• Updating language in the existing prescriber or pharmacy training materials to reflect approved safety labeling changes made to the WARNINGS and PRECAUTIONS sections of the package insert. • Addition of newly approved language from the product labeling describing new adverse reactions and drug-drug interactions to the REMS patient education brochure
Changes that *are not considered conforming* (i.e., overall programmatic and/or implementation changes to the REMS that result from approved (or ordered) safety labeling changes (180-day review))	• Addition of a new ETASU[a] requiring the documentation of safe-use conditions, based on the newly approved language in the BOXED WARNING and CONTRAINDICATIONS sections of the package insert • Addition of a new Dear Health Care Provider Letter to the REMS materials that describes a new serious risk added to the product labeling • Extensive changes to prescriber training materials to add new patient monitoring procedures necessary to address a new serious risk described in approved product labeling

[a] ETASU = elements to assure safe use

IV. SUBMISSION PROCEDURES

This section provides an overview of submission procedures that apply to all REMS changes (revisions and modifications). The Appendix summarizes the relevant information that should be included in these submissions.[19]

[18] See section IV., Submission Procedures.

[19] The Electronic Submissions Gateway web page (https://www.fda.gov/industry/electronic-submissions-gateway) provides email addresses to which application holders can send questions about electronic submissions (e.g., location of REMS materials in the electronic common technical document) and general questions about sending electronic submissions through the electronic submissions gateway. Application holders also can refer to the guidance for industry *Providing Regulatory Submissions in Electronic Format — General Considerations* (January 1999).

A. General Considerations

When the FDA requires a REMS change,[20] the FDA will describe the required change and the type of submission that is needed (CBE-30 supplement or PAS).

Application holders who wish to seek advice from the FDA before submission of a proposed REMS modification may do so in accordance with established FDA procedures.[21]

B. Content and Format

1. Administrative Content

Submissions should include:

a) The appropriate submission identifier in bold capital letters at the top of the first page of the submission and completed Form FDA 356h (see the Appendix).

b) A detailed description of the REMS changes to allow the FDA to determine quickly if the appropriate submission category has been used. This information can be included in the submission or the cover letter.

c) A clean (without track changes) Word version of the changed REMS and REMS materials.

d) A redlined (track changes) Word version of the changed REMS and REMS materials.

e) One PDF file that includes a clean version of the changed REMS document and REMS materials.

f) A clean (without track changes) Word version of the updated REMS Supporting Document[22] to align with changes made to the REMS document and REMS materials, as appropriate.

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[20] See section 505-1(g)(4)(B) of the FD&C Act.

[21] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017) (when final, this guidance will represent the FDA's current thinking on this topic). Application holders seeking FDA advice about proposed modifications to REMS for drugs approved under an ANDA should contact the Office of Bioequivalence in the Office of Generic Drugs in CDER (see section VI., Contact Information).

[22] The REMS Supporting Document expands on information in the REMS document and provides additional information about the REMS, such as the rationale for, and supporting information about, the design, implementation, and assessment of the REMS. See the draft guidance for industry *Format and Content of a REMS Document* (October 2017). When final, this guidance will represent the FDA's current thinking on this topic. The statutory requirements for REMS revisions and modifications do *not* apply to the REMS Supporting Document (i.e., changes to the REMS supporting document are neither REMS revisions nor modifications).

g) A redlined (track changes) Word version of the updated REMS Supporting Document.

h) A REMS history of all changes to the REMS since originally approved (see section IV.B.2., REMS History).

i) **For REMS modifications only:** An adequate rationale for the proposed modifications (see section IV.B.3., Adequate Rationale for REMS Modifications).

2. REMS History

For all REMS changes, the FDA recommends application holders include a REMS history that outlines all changes made to the REMS since its original approval.

The REMS history should be similar in format to the history of labeling changes provided in submissions containing new labeling.[23,24] The REMS history should be in a tabular format that lists all approved and/or pending REMS changes with the approval or submission date, respectively, a summary of the changes (revisions and/or modifications), and a list of affected REMS materials.

3. Adequate Rationale for REMS Modifications

All proposed REMS modifications (minor or major) initiated by the application holder must include an *adequate rationale*.[25] The rationale may include, but is not limited to, the reason(s) why the proposed modification is necessary; the potential effect of the proposed modification on how the REMS addresses the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. If a REMS assessment was submitted in the previous 18 months and includes data to support the proposed change, then it can be referenced as the adequate rationale.

When considering a proposed REMS modification as part of an efficacy supplement for a new indication for use (see section IV.C., Submission of Proposed REMS Changes), the REMS assessment that is required in accordance with section 505-1(g)(2)(A) of the FD&C Act will be considered the adequate rationale to support the proposed REMS modification. This adequate rationale should include:

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[23] See the eCTD Technical Conformance Guide, Technical Specifications Document. This document is incorporated by reference in the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (January 2019).

[24] For an example of a REMS history, see the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions* (November 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[25] See section 505-1(g)(4)(A) of the FD&C Act.

- *In every case:* An evaluation of how the benefit-risk profile will or will not change with the new indication and the implications of any changes on the currently approved REMS

- *If the new, proposed indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS

- *If the proposed REMS modification is based on a change in the benefit-risk profile or because of the new indication of use:* Explanation of the reason(s) why the proposed REMS modification is necessary; the potential effect of the proposed changes on how the REMS addresses the serious risk(s) for which the program was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change

- *If a REMS assessment was submitted in the 18 months before submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment

- *If a REMS assessment was not submitted in the 18 months before submission of the supplemental application for a new indication for use:* Include as many of the currently listed assessment plan items as feasible

If the proposed REMS modifications are submitted in accordance with an FDA requirement to modify the REMS,[26] submission of an adequate rationale is not required as long as the proposed changes are identical to or consistent with those specified by the FDA. If the proposed REMS modification supplement includes changes that differ from the modifications described by the FDA, an adequate rationale is required for those proposed changes in accordance with section 505-1(g)(4)(A) of the FD&C Act.

If the proposed REMS modifications are due to approved safety labeling changes, or to safety labeling changes that the FDA has ordered the application holder to make, the adequate rationale can consist of a statement that the REMS changes are submitted due to the approved or ordered safety labeling changes (see section V.D., REMS Modification Due to Safety Labeling Changes).

C. Submission of Proposed REMS Changes

Revisions should be submitted as "REMS Revision," a submission type similar to drug correspondence. REMS revisions should be documented in the next annual report[27] *and* submitted at the time the revisions are implemented so that the current REMS document and

[26] See section 505-1(g)(4)(B) of the FD&C Act.

[27] A summary of REMS revisions should be included under section c of the next NDA, BLA, or ANDA annual report (21 CFR 314.81(b)(2)(iii)(c)).

REMS materials are publicly displayed on the FDA web page of approved REMS.[28,29] Because REMS revisions are not submitted as supplemental applications, they do not require FDA action, and can be implemented following receipt by the FDA.

Proposed *minor* REMS modifications should be submitted as a CBE-30 supplement; proposed *major* modifications should be submitted as a PAS.

Proposed REMS modifications submitted to conform a REMS to approved or ordered safety labeling changes are major modifications and should be submitted as a PAS. However, these modifications are subject to a different time frame for review than other major modifications and safety labeling changes supplements submitted under section 505(o)(4) (see section V.D., REMS Modification Due to Safety Labeling Changes).

Application holders can submit multiple proposed REMS modifications of the same type (e.g., multiple minor modifications) in a single submission.

Application holders also can submit a single submission that contains REMS changes of different types (e.g., REMS revisions and minor (or major) modifications; or minor modifications and major modifications). However, a single submission with multiple REMS changes will affect the time frame for review of the submission (see section V.E., Submissions Containing More Than One Type of REMS Change).

A REMS assessment, supplemental efficacy application, or a supplemental CMC application may result in changes to an approved REMS.[30] REMS modifications included in these applications should include the relevant information for the submission and should be submitted according to the instructions described in the Appendix.

V. FDA TIME FRAMES[31] FOR REMS CHANGES

The FDA will promptly assess submissions that contain proposed REMS changes to determine whether the proposed changes meet the criteria for the type of submission used (i.e., CBE-30 for minor REMS modifications or a PAS for major REMS modifications, including REMS modifications due to safety labeling changes). If the FDA determines that the REMS changes are not appropriately categorized and submitted, the FDA will notify the application holder, in

[28] See section 505-1(h)(2)(C) of the FD&C Act.

[29] See the FDA web page Approved Risk Evaluation and Mitigation Strategies (REMS) — REMS@FDA, available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

[30] Examples of REMS modifications that may result from efficacy supplements include addition of a new dosing regimen, or a new indication for use (see Tables 2 and 3). An example of a REMS modification that may result from a CMC supplement is addition of a new packaging to the REMS document and/or the appended REMS materials.

[31] The time frames described in this section refer to calendar days.

writing, within 14 days of receipt of the submission, and as described in the following subsections.

A. REMS Revisions

REMS revisions are not submitted as supplemental applications; therefore, they do not require FDA action. Application holders can implement REMS revisions following receipt by the FDA.

B. Minor REMS Modifications

The FDA will review and act on proposed minor REMS modifications within 60 days of receipt.[32] Although the application holder can implement the modified REMS 30 days after receipt by the FDA, the changes to the REMS are not considered final until approved by the FDA.

If the FDA informs the application holder (within 14 days of receipt) that information necessary for the FDA to act on the submission is missing, the application holder should delay implementation. The missing information should be submitted as soon as possible, but no later than 10 days after notification. If the missing information is not received within 10 days of the FDA request, the FDA may issue a complete response letter.

C. Major REMS Modifications

The FDA will review and act on proposed major REMS modifications within 180 days of receipt.[33] Proposed major REMS modifications must not be implemented before FDA approval.[34]

D. REMS Modification Due to Safety Labeling Changes

The FDA will review and act on proposed *conforming REMS modifications* within 60 days of receipt and will review and act on *modifications not considered conforming* within 180 days of receipt. Proposed major REMS modifications, including modifications due to safety labeling changes, must not be implemented before FDA approval.[35]

The 60- or 180-day review time frame does not begin until the FDA receives the REMS modification to conform or align with the approved (or ordered) safety labeling changes. Even if

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[32] See section 505-1(h)(2)(A)(ii) of the FD&C Act.

[33] See section 505-1(h)(2)(A)(i) of the FD&C Act. The 180-day review time frame does not apply if the dispute resolution process described in section 505-1(h)(4) applies.

[34] See 21 CFR 314.70(b) and 21 CFR 601.12(b)(3) and (f)(1).

[35] See 21 CFR 314.70(b)(3). It is the FDA's view that the labeling changes process under 21 CFR 314.70 and 601.12 continues to be available to application holders in situations in which application holders become aware of newly acquired information, including in circumstances that meet the criteria for submission of a CBE-0.

a REMS modification due to a safety labeling changes supplement is submitted at the same time as the corresponding proposed safety labeling changes, or after submission but before the approval of the labeling supplement (see section IV.C., Submission of Proposed REMS Changes), the 60- or 180-day review time frame does not begin until the associated labeling supplement is approved (or ordered)[36] and the REMS modification supplement is amended, if necessary, to accurately reflect the approved labeling.

E. Submissions Containing More Than One Type of REMS Change

Because the FDA takes one action per supplement, submissions that contain REMS changes of different types will be reviewed and acted on based on the time frame for the longer review clock. Therefore, the FDA will review and act on submissions that include both minor and major REMS modifications within 180 days of receipt (to allow sufficient time for review of the major modifications). The FDA will review and act on submissions containing both minor modifications and REMS revisions within 60 days (to allow sufficient time for review of the minor modifications).

F. REMS Modifications Included in Other Submissions

Proposed REMS modifications submitted with a REMS assessment required in accordance with the timetable for submission of assessments of the REMS will be reviewed concurrently with the REMS assessments. Action on the proposed REMS modifications will follow review of the REMS assessment.

Proposed REMS modifications submitted in an efficacy or CMC supplement will be reviewed and acted on as part of that supplement, and not according to the time frames described above.[37] REMS modifications submitted as part of an efficacy or CMC supplement may not be implemented until approved.

G. Posting Revised and Modified REMS on the FDA Website

The FDA intends to post updated REMS reflecting REMS revisions on the website within 14 days of receipt of the submission. [38]

The FDA intends to post updated REMS reflecting REMS modifications on the website within 3 days of approval.

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[36] See section 505-1(h)(2)(A)(iii) of the FD&C Act.

[37] For more information on the FDA's review of efficacy supplements, see the guidance for industry *Standards for the Prompt Review of Efficacy Supplements, Including Priority Efficacy Supplements* (May 1998). For more information on the FDA's review of CMC supplements, see the guidance for industry *Changes to an Approved NDA or ANDA* (April 2004).

[38] See https://www.accessdata.fda.gov/scripts/cder/rems/.

VI. CONTACT INFORMATION

The contacts for questions about a proposed REMS revision or modification are as follows:

- **Center for Drug Evaluation and Research:**
  - For a drug under an NDA or BLA: the regulatory project manager in the Office of New Drugs review division responsible for that drug
  - For a drug under an ANDA: the REMS coordinator in the Office of Bioequivalence in the Office of Generic Drugs
  - For modifications of SS REMS: the regulatory project manager in the Project Management Staff, Office of Surveillance and Epidemiology
- **Center for Biologics Evaluation and Research:**
  - The regulatory project manager in the office responsible for that drug

APPENDIX:
SUBMISSION PROCEDURES FOR CHANGES TO APPROVED REMS

Table A summarizes the relevant information to include in submissions for changes (revisions and modifications) to approved risk evaluation and mitigation strategies (REMS).

Table A: Information to Include in Submissions of Proposed REMS Changes

Type of REMS Change/ Submission Type	Submission Identifier	Instructions for Completing Form FDA 356h[1]	Other Administrative Content[2]	REMS History[3]	Adequate Rationale[4]
REMS Revision	**REMS REVISION**	**Field 21** – Select "Other" and enter "REMS Revision" **Field 25** – Enter "REMS Revision"	Items[5] b-h	Recommended	Not required
Minor REMS Modification	**NEW SUPPLEMENT FOR [NDA/BLA/ ANDA][6] [assigned #]** **CHANGES BEING EFFECTED IN 30 DAYS** **PROPOSED MINOR REMS MODIFICATION**	**Field 21** – Select "REMS Supplement" **Field 23** – Select "CBE-30" **Field 25** – Enter "Proposed Minor REMS Modification"	Items b-i	Recommended	Required

continued

Table A, continued

Type of REMS Change/ Submission Type	**Submission Identifier**	**Instructions for Completing Form FDA 356h[1]**	**Other Administrative Content[2]**	**REMS History[3]**	**Adequate Rationale[4]**
Major REMS Modification	**NEW SUPPLEMENT FOR [NDA/BLA/ANDA] [assigned #]** **PRIOR APPROVAL SUPPLEMENT** **PROPOSED MAJOR REMS MODIFICATION**	**Field 21** – Select "REMS Supplement" **Field 23 –** Select "Prior Approval (PA)" **Field 25** – Enter "Proposed Major REMS Modification"	Items b-i	Recommended	Required
REMS Modification Due to Safety Labeling Changes (Major REMS Modification)	**NEW SUPPLEMENT FOR [NDA/BLA/ANDA] [assigned #]** **PRIOR APPROVAL SUPPLEMENT** **PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT [supplement #]**	**Field 21** – Select "REMS Supplement" **Field 23 –** Select "Prior Approval (PA)" **Field 25** – Enter "Proposed REMS Modification Due to Safety Labeling Changes Submitted in Supplement [supplement #]"	Items b-i	Recommended	Required

continued

Table A, continued

Type of REMS Change/ Submission Type	**Submission Identifier**	**Instructions for Completing Form FDA 356h[1]**	**Other Administrative Content[2]**	**REMS History[3]**	**Adequate Rationale[4]**
Multiple Types of REMS Changes in Same Submission	**NEW SUPPLEMENT FOR [NDA/BLA/ANDA] [assigned #]** **PRIOR APPROVAL SUPPLEMENT** **OR CHANGES BEING EFFECTED IN 30 DAYS** **PROPOSED REMS MODIFICATIONS**	**Field 21** – Select "REMS Supplement" **Field 23** – Select "Prior Approval (PA)" **or** "CBE-30" **Field 25** – Enter "Proposed REMS Modification"	Items b-i	Recommended	Required

continued

Table A, continued

Type of REMS Change/ Submission Type	**Submission Identifier**	**Instructions for Completing Form FDA 356h[1]**	**Other Administrative Content[2]**	**REMS History[3]**	**Adequate Rationale [4]**
Efficacy Supplement With Proposed REMS Modifications	**NEW SUPPLEMENT FOR [NDA/BLA] [assigned #]** **PRIOR APPROVAL SUPPLEMENT** < other supplement identification > **[EFFICACY SUBMISSION CONTENT INFORMATION]** **PROPOSED REMS MODIFICATION**	**Field 21** – Select "Efficacy Supplement" **and** "REMS Supplement" **Field 23** – Select "Prior Approval (PA)" **Field 25** – Enter "Efficacy Supplement" **and** "Proposed REMS Modification"	Items b-i	Recommended	Required

continued

Table A, continued

Type of REMS Change/ Submission Type	**Submission Identifier**	**Instructions for Completing Form FDA 356h[1]**	**Other Administrative Content[2]**	**REMS History[3]**	**Adequate Rationale[4]**
CMC[6] Supplement With Proposed REMS Modifications	**NEW SUPPLEMENT FOR [NDA/BLA/ANDA] [assigned #]** **PRIOR APPROVAL SUPPLEMENT or CHANGES BEING EFFECTED in 30 Days** < other supplement identification > **[CMC SUBMISSION CONTENT INFORMATION]** **PROPOSED REMS MODIFICATION**	**Field 21** – Select "CMC Supplement" **and** "REMS Supplement" **Field 23** – Select "CBE-30" **or** "Prior Approval (PA)" **Field 25** – Enter "CMC Supplement **and** "Proposed REMS Modification"	Items b-i	Recommended	Required

continued

Table A, continued

Type of REMS Change/ Submission Type	Submission Identifier	Instructions for Completing Form FDA 356h[1]	Other Administrative Content[2]	REMS History[3]	Adequate Rationale[4]
REMS Assessment With Proposed REMS Modifications	**NEW SUPPLEMENT FOR [NDA/BLA/ANDA]** [assigned #] **PRIOR APPROVAL SUPPLEMENT or CHANGES BEING EFFECTED in 30 Days** **REMS MODIFICATION/ REMS ASSESSMENT**	**Field 21** – Select "REMS Supplement" **and** "Other"; then enter "REMS Assessment" **Field 23** – Select "CBE-30" **or** "Prior Approval (PA)" **Field 25** – Enter "REMS Assessment" **and** "Proposed REMS Modification"	Items b-i	Recommended	Required: The required REMS assessment included with the supplement is considered the adequate rationale

[1] The field numbers in this column correspond to the number boxes on Form FDA 356h.

[2] See section IV.B.1., Administrative Content, of the guidance.

[3] See section IV.B.2., REMS History, of the guidance.

[4] See section IV.B.3., Adequate Rationale for REMS Modifications, of the guidance.

[5] Items as listed in section IV.B.1., Administrative Content, of the guidance.

[6] NDA = new drug application; BLA = biologics license application; ANDA = abbreviated new drug application; CMC = chemistry, manufacturing, and controls