United States Court of Appeals for the Fifth Circuit

United States Court of Appeals
Fifth Circuit
FILED
April 12, 2023
Lyle W. Cayce
Clerk

No. 23-10362

ALLIANCE FOR HIPPOCRATIC MEDICINE; AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS; AMERICAN COLLEGE OF PEDIATRICIANS; CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS; SHAUN JESTER, D.O.; REGINA FROST-CLARK, M.D.; TYLER JOHNSON, D.O.; GEORGE DELGADO, M.D.,

Plaintiffs—Appellees,

versus

FOOD & DRUG ADMINISTRATION; ROBERT M. CALIFF, *Commissioner of Food and Drugs*; JANET WOODCOCK, M.D., *in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration*; PATRIZIA CAVAZZONI, M.D., *in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration*; UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, *Secretary, U.S. Department of Health and Human Services*,

Defendants—Appellants,

versus

DANCO LABORATORIES, L.L.C.,

Intervenor—Appellant.

Appeal from the United States District Court
for the Northern District of Texas
USDC No. 2:22-CV-223

UNPUBLISHED ORDER

Before HAYNES,* ENGELHARDT, and OLDHAM, *Circuit Judges*.

PER CURIAM:

For the reasons given below, IT IS ORDERED that defendants' motions for a stay pending appeal are GRANTED IN PART. At this preliminary stage, and based on our necessarily abbreviated review, it appears that the statute of limitations bars plaintiffs' challenges to the Food and Drug Administration's approval of mifepristone in 2000. In the district court, however, plaintiffs brought a series of alternative arguments regarding FDA's actions in 2016 and subsequent years. And the district court emphasized that its order separately applied to prohibit FDA's actions in and after 2016 in accordance with plaintiffs' alternative arguments. As to those alternative arguments, plaintiffs' claims are timely. Defendants have not shown that plaintiffs are unlikely to succeed on the merits of their timely challenges. For that reason, and as more fully explained below, defendants' motions for a stay pending appeal are DENIED IN PART. Defendants' alternative motions for an administrative stay are DENIED AS MOOT. Plaintiffs' motion to dismiss the appeal is DENIED. The appeal is EXPEDITED to the next available Oral Argument Calendar.

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* JUDGE HAYNES concurs only in part: she concurs in the grant of the expedited appeal and the denial of the motion to dismiss. With respect to the request for a stay of the district court's order, as a member of the motions panel, she would grant an administrative stay for a brief period of time and defer the question of the stay pending appeal to the oral argument merits panel which receives this case.

I.

A.

Congress delegated to the Food and Drug Administration ("FDA") the responsibility to ensure that "new drugs" are "safe and effective." 21 U.S.C. §§ 321(p), 355; *see also id.* § 393(b)(2)(B). When making its approval determination, FDA evaluates whether a new drug application ("NDA") includes scientific evidence demonstrating that the drug is safe and effective for its intended uses. *Id.* § 355(d); *see also* 21 C.F.R. §§ 314.50, 314.105(c). Similarly, when a sponsor submits a supplemental new drug application ("SNDA") proposing changes to the conditions of approval for a drug (such as changes to a drug's labeling or FDA-imposed restrictions), FDA reviews the scientific evidence to support the changes. *See* 21 C.F.R. § 314.70. To approve a generic version of a previously approved drug, FDA reviews whether an abbreviated new drug application ("ANDA") contains information showing that the proposed generic drug is materially the "same" as the approved drug. 21 U.S.C. § 355(j)(2).

In 1992, FDA promulgated the so-called "Subpart H" regulations. Subpart H accelerates approval of drugs "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (*e.g.*, ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)." 21 C.F.R. § 314.500. Originally, Subpart H was intended to promote rapid approval for life-saving HIV-AIDS drugs. But given that Subpart H approvals were accelerated, FDA recognized that it would need *post*-approval safety measures. These post-approval safety measures would "assure safe use" of the quickly approved Subpart H drugs. *Id.* § 314.520. In 2007, Congress ratified these post-approval safety measures as "risk evaluation and

mitigation strategies" ("REMS"), which "ensure that the benefits of the drug outweigh the risks." 21 U.S.C. § 355-1(a)(1)–(2).

B.

In 2000, FDA approved mifepristone to be marketed with the brand name Mifeprex under Subpart H (the "2000 Approval"). *See* 21 C.F.R. § 314.500; FDA Add. 181.[1] In the 2000 Approval, FDA concluded that pregnancy is a "life-threatening illness," triggering an accelerated approval of mifepristone under Subpart H. FDA Add. 186. FDA also concluded that a variety of post-approval restrictions on Mifeprex were required "to assure safe use." 21 C.F.R. § 314.520. As noted in the previous section, today we call such post-approval restrictions "REMS." The 2000 Approval imposed several REMS, including: (1) limiting the drug to pregnant women and girls for use through 49 days gestation; (2) requiring three in-person office visits, the first to administer mifepristone, the second to administer misoprostol, and the third to assess any complications and ensure there were no fetal remains in the womb; (3) requiring the supervision of a qualified physician; and (4) requiring the reporting of all adverse events from the drugs. FDA Add. 181–91. FDA granted Danco Laboratories, LLC, an exclusive license to manufacture, market, and distribute Mifeprex in the United States. FDA Add. 109.

In 2002, two of the plaintiff associations in this case filed a citizen petition challenging the 2000 Approval (the "2002 Citizen Petition"). *See* 21 C.F.R. § 10.25(a); PI App. 280–375. Roughly fourteen years later, FDA denied the 2002 Citizen Petition (the "2016 Petition Denial"). FDA Add.

[1] Citations to the addendum to FDA's emergency motion for a stay pending appeal are denoted "FDA Add." Citations to the appendix to plaintiffs' motion for a preliminary injunction are denoted "PI App."

804–36. And on the very same day in March 2016, FDA approved several major changes to mifepristone's approved conditions of use, including its REMS. Specifically, FDA removed four of the original safety restrictions by (1) increasing the maximum gestational age at which a woman can use the drug from 49 to 70 days; (2) reducing the number of required in-person office visits from three to one; (3) allowing non-doctors to prescribe and administer the chemical abortions drugs; and (4) eliminating the requirement for prescribers to report non-fatal adverse events from chemical abortion (the "2016 Major REMS Changes"). FDA Add. 777–802.

In March 2019, one of the plaintiff associations filed a second citizen petition challenging the 2016 Major REMS Changes (the "2019 Citizen Petition"). FDA Add. 192–217. That petition asked FDA to "restore" the 2000 Approval's REMS and "retain" a requirement that mifepristone be dispensed to patients in person. FDA Add. 192.

In April 2019, FDA approved GenBioPro, Inc's ANDA for a generic version of mifepristone (the "2019 Generic Approval"). PI App. 694–708. GenBioPro's generic version of mifepristone has the same labeling and REMS requirements as Danco's Mifeprex.

In April 2021, FDA announced that it would "exercise enforcement discretion" to allow "dispensing mifepristone through the mail . . . or through a mail-order pharmacy" during the COVID-19 pandemic (the "2021 Mail-Order Decision"). PI App. 713–15. FDA took this action in response to a letter from the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine. PI App. 710–11.

Later that year, in December 2021, FDA denied almost all of the 2019 Citizen Petition (the "2021 Petition Denial"). FDA Add. 837–76. In particular, FDA expressly rejected the 2019 Citizen Petition's request to keep the in-person dispensing requirements and announced that the agency

had concluded that "the in-person dispensing requirement is no longer necessary." FDA Add. 842.

Finally, in January 2023, FDA approved a modified REMS for mifepristone lifting the in-person dispensing requirement. *See REMS Single Shared System for Mifepristone 200 mg* (Jan. 2023), https://perma.cc/MJT5-35LF (the "2023 Mail-Order Decision").[2]

C.

In November 2022, plaintiffs (physicians and physician organizations) filed this suit against FDA, HHS, and a several agency heads in the official capacities. Plaintiffs first challenged FDA's 2000 Approval of the drug. But they also requested multiple grounds of alternative relief for FDA's subsequent actions. Immediately after filing, plaintiffs moved for a preliminary injunction ordering FDA to withdraw or suspend (1) FDA's 2000 Approval and 2019 Generic Approval, (2) FDA's 2016 Major REMS Changes, and (3) FDA's 2021 Mail-Order Decision and its 2021 Petition Denial of the 2019 Citizen Petition. If that's confusing, we hope this chart helps:

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[2] Danco suggests the 2023 Mail-Order Decision moots part of plaintiffs' claims. *See* Danco Stay App. 22. We disagree. The Supreme Court has explicitly instructed this court to review a new agency action finalized after litigation commenced and while the appeal was pending because this decision was a "final agency action" for purposes of 5 U.S.C. § 704. *Biden v. Texas*, 142 S. Ct. 2528, 2544-45 (2022) (quotation omitted).

Event	Citation	Description
2000 Approval	FDA Add. 181–91	Approved mifepristone with these REMS: (1) pregnancies under 50 days gestation; (2) three in-person office visits; (3) supervision of a qualified physician; and (4) reporting of all adverse events
2002 Citizen Petition	PI App. 280–375	Plaintiffs' challenge to 2000 Approval
2016 Petition Denial	FDA Add. 804–36	FDA denial of 2002 Citizen Petition
2016 Major REMS Changes	FDA Add. 768, 777–802	FDA changed four of the 2000 Approval's REMS: (1) increased maximum gestational age to 70 days; (2) reduced required in-person office visits to one; (3) allowed non-doctors to prescribe and administer mifepristone; and (4) eliminated reporting of non-fatal adverse events
2019 Citizen Petition	FDA Add. 192–217	Plaintiffs' challenge to 2016 Major REMS Changes
2019 Generic Approval	PI App. 694–708	FDA ANDA Approval Letter for mifepristone generic to GenBioPro, Inc.
2021 Mail-Order Decision	PI App. 713–15	FDA announces "enforcement discretion" to allow mifepristone to be dispensed through the mail during COVID-19
2021 Petition Denial	FDA Add. 837–76	FDA denial of almost all of the 2019 Citizen Petition, including plaintiffs' request to keep the in-person dispensing requirements
2023 Mail-Order Decision	https://perma.cc/MJT5-35LF	FDA permanently removed the in-person dispensing REMS

On April 7, 2023, the district court entered an order staying the effective date of the 2000 Approval and each of the subsequent challenged actions.[3] The district court stayed its own order for seven days to allow the defendants time to appeal.

II.

FDA and Danco ("stay applicants" or "applicants") ask us to stay the district court's order pending appeal. Our power to grant a stay is inherent. *See In re McKenzie*, 180 U.S. 536, 551 (1901); *Scripps-Howard Radio v. FCC*, 316 U.S. 4, 10–14 (1942). It's also statutory. *See* FED. R. APP. P. 8; 28 U.S.C. § 1651; 5TH CIR. R. 27.3; *see also* 16A CHARLES ALAN WRIGHT & ARTHUR R. MILLER, FEDERAL PRACTICE & PROCEDURE § 3954 (5th ed. Apr. 2022 update).

But we grant stays "only in extraordinary circumstances." *Williams v. Zbaraz*, 442 U.S. 1309, 1311 (1979) (Stevens, J., in chambers); *see also Graves v. Barnes*, 405 U.S. 1201, 1203 (1972) (Powell, J., in chambers) (same); *Ruckelshaus v. Monsanto Co.*, 463 U.S. 1315, 1316 (1983) (Blackmun, J., in chambers) (same). This rule reflects the fact that "a stay is not a matter of right, even if irreparable injury might otherwise result." *Virginian Ry. Co. v. United States*, 272 U.S. 658, 672 (1926). Instead, a stay requires "an exercise of judicial discretion." *Ibid.* A "decree creates a strong presumption of its own correctness," which often counsels against a stay. *Id.* at 673.

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[3] As both parties recognize, this order would have the practical effect of an injunction because it would remove mifepristone from the market. Plaintiffs filed a motion to dismiss applicants' appeal on the theory that § 705 stays are not sufficient to trigger our interlocutory appellate jurisdiction under 28 U.S.C. § 1292(a). We disagree. *See Abbott v. Perez*, 138 S. Ct. 2305, 2319–20 (2018) (explaining that the "practical effect" test of 28 U.S.C. §§ 1292(a)(1) and 1293 "prevents [the] manipulation" that could occur "if the availability of interlocutory review depended on the district court's use of the term 'injunction'").

The Supreme Court has prescribed "four traditional stay factors" that govern this equitable discretion in most civil cases. *Ala. Ass'n of Realtors v. HHS*, 141 S. Ct. 2485, 2487 (2021) (quotation omitted); *see also Hilton v. Braunskill*, 481 U.S. 770, 776–77 (1987); *Rose v. Raffensperger*, 143 S. Ct. 58, 59 (2022) (reversing stay of an injunction after the court of appeals failed to analyze the traditional stay factors). Those factors are:

> (1) whether the stay applicant has made a strong showing that he is likely to succeed on the merits; (2) whether the applicant will be irreparably injured absent a stay; (3) whether issuance of the stay will substantially injure the other parties interested in the proceeding; and (4) where the public interest lies.

Nken v. Holder, 556 U.S. 418, 426 (2009) (quoting *Hilton*, 481 U.S. at 776); *see also Whole Woman's Health v. Jackson*, 141 S. Ct. 2494, 2495 (2021). Although no factor is dispositive, the likelihood of success and irreparable injury factors are "the most critical." *Nken*, 556 U.S. at 434. Success on either factor requires that the stay seeker make a strong not merely "possib[le]" showing. *Ibid.*

In these respects, stays might appear identical to preliminary injunctions. Similar factors govern both and both require an "extraordinary" deployment of judicial discretion. *Winter v. Nat. Res. Def. Council*, 555 U.S. 7, 24 (2008). But the two are not "one and the same." *Nken*, 556 U.S. at 434. A stay "operates upon the judicial proceeding itself," not on the conduct of a particular actor. *Id.* at 428. And, once one party has won an injunction, proof burdens reverse. It is the enjoined party who seeks a stay, or FDA and Danco here, who must carry the burden of proving that the *Nken* factors command us to issue one. *See Landis v. N. Am. Co.*, 299 U.S. 248, 255 (1936).

If the stay applicants show that circumstances require a stay of some but not all of the district court's order, we may, in our discretion, "tailor a stay so that it operates with respect to only some portion of the proceeding."

Trump v. Int'l Refugee Assistance Project, 137 S. Ct. 2080, 2087 (2017) (per curiam) (quoting *Nken*, 556 U.S. at 428).

We find that FDA and Danco succeed only in part.

III.

Regarding likelihood to succeed on the merits, the stay applicants raise four arguments. They contend (A) plaintiffs are unlikely to defend the district court's stay because they lack standing. They next contend (B) plaintiffs' claims are untimely. Then they claim (C) plaintiffs' claims are unexhausted. Finally, applicants contend (D) FDA's actions are not arbitrary, capricious, or otherwise contrary to law. We consider each in turn.

A.

We begin with Article III standing. To bring their claims in federal court, plaintiffs must satisfy the familiar tripartite test: they must show they suffered an injury in fact, that's fairly traceable to the defendants, and that's likely redressable by a favorable decision. *See Lujan v. Nat'l Wildlife Fed'n*, 497 U.S. 871 (1990). Importantly, only one plaintiff needs to have standing to present a valid case or controversy. *See Rumsfeld v. Forum for Acad. & Institutional Rts., Inc.*, 547 U.S. 47, 52 n.2 (2006).

Plaintiffs and the district court offered numerous theories of standing. At this preliminary, emergency stage, we are unpersuaded by applicants' contentions that all of these theories fail to create a justiciable case or controversy. We need only consider two: (1) injuries to doctors and (2) injuries to the plaintiff medical associations.[4]

[4] We are cognizant of the fact that the Supreme Court has disavowed the theories of third-party standing that previously allowed doctors to raise patients' claims in abortion

1.

First, it appears that the individual plaintiffs and doctors in plaintiff associations have standing to challenge FDA's actions.

To allege an injury in fact, these doctors must show they have suffered an "invasion of a legally protected interest" that is both "concrete and particularized" and "actual or imminent, not conjectural or hypothetical." *Spokeo, Inc. v. Robins*, 578 U.S. 330, 339 (2016) (quotation omitted). Plaintiffs must identify specific injuries that go beyond "general averments" or "conclusory allegations." *Friends of the Earth, Inc. v. Laidlaw Env't Servs. (TOC), Inc.*, 528 U.S. 167, 184 (2000) (quoting *Lujan*, 497 U.S. at 888). Where a plaintiff seeks prospective relief and hence points to future injuries, the Supreme Court has emphasized that "threatened injury must be *certainly impending* to constitute injury in fact, and that allegations of *possible* future injury are not sufficient." *Clapper v. Amnesty Int'l USA*, 568 U.S. 398, 409 (2013) (quotation omitted).

Here, FDA-approved the "Patient Agreement Form," which is part of the REMS for mifepristone, provides:

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cases. *See Dobbs v. Jackson Women's Health Org.*, 142 S. Ct. 2228, 2275 & n.61 (2022). So we express no opinion on plaintiffs' third-party standing theories.

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take mifepristone on Day 1.
   b. I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am "feeling sick," including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

2023 Mail-Order Decision at 10. FDA thus cannot deny that serious complications from mifepristone are certainly impending. Those complications are right there on the "Patient Agreement Form" that FDA itself approved and that Danco requires every mifepristone user to sign. According to the applicants, more than 5,000,000 women have taken this drug since the 2000 Approval. FDA Stay App. 1. That means that, again according to the applicants' own information, between 100,000 (2%) and

350,000 (7%) of mifepristone users had unsuccessful chemical abortions and had to "talk with [their] provider[s] about a surgical procedure to end [their] pregnanc[ies]." 2023 Mail-Order Decision at 10. And where did those hundreds of thousands of women go for their "surgical procedures"? Again, we need not speculate because the 2016 Major REMS Changes, the 2021 Petition Denial, and the 2023 Mail-Order Decision all allow non-doctors to prescribe mifepristone. The women who use this drug cannot possibly go back to their non-doctor-prescribers for surgical abortions, so again, as the "Patient Agreement Form" itself says, they must instead seek "emergency care" from a qualified physician.

The plaintiff emergency room doctors have a concrete, particularized injury since they have provided—and with certainty will continue to provide—the "emergency care" that applicants specified in the "Patient Agreement Form." PI App. 167, 169, 194, 206. Mifepristone users who present themselves to the plaintiffs have required blood transfusions, overnight hospitalization, intensive care, and even surgical abortions. PI App. 205–06. As one doctor testified:

> For example, in one month while covering the emergency room, my group practice admitted three women to the hospital. Of the three women admitted in one month due to chemical abortion complications, one required admission to the intensive care unit for sepsis and intravenous antibiotics, one required a blood transfusion for hemorrhage, and one required surgical completion for the retained products of conception (*i.e.*, the doctors had to surgically finish the abortion with a suction aspiration procedure).

PI App. 206.

Another doctor testified:

> [O]ne of my patients had obtained mifepristone and misoprostol from a website, without an in-person

> visit. . . . After taking the chemical abortion drugs, she began having very heavy bleeding followed by significant abdominal pain and a fever. When I saw her in the emergency room, she had evidence of retained pregnancy tissue along with endometritis, an infection of the uterine lining. She also had acute kidney injury, with elevate creatinine. She required a dilation and curettage (D&C) surgery to finish evacuating her uterus of the remaining pregnancy tissue and hospitalization for intravenous (IV) antibiotics, IV hydration, and a blood transfusion. I spent several hours with her the day of her surgery/hospital admission, keeping me from my primary patient responsibilities in the labor and delivery unit and requiring me to call in an additional physician to help cover those responsibilities.

PI App. 194–95. As a result of FDA's failure to regulate this potent drug, these doctors have had to devote significant time and resources to caring for women experiencing mifepristone's harmful effects. This harm is sufficiently concrete.

A second independent injury from the adverse effects of mifepristone is the "enormous stress and pressure" physicians face in treating these women. PI App. 215. One doctor said the strain "is some of the most emotionally taxing work I have done in my career." PI App. 880. Thus, this is an independent injury because FDA's actions "significantly affect[]" the doctors' "quality of life." *Sierra Club v. Morton*, 405 U.S. 727, 734–35 (1972).

The doctors offered specific facts to explain this stress. Women who take these drugs are susceptible to "torrential bleeding." PI App. 170, 215. In fact, "the risk of severe bleeding with chemical abortion is five times higher than from surgical abortion." PI App. 879. And these situations can quickly go from bad to worse. As one doctor testified:

> One of my patients, who was about nine weeks pregnant, had previously been treated by hospital staff for a pulmonary

> embolism with anti-coagulants. She was advised that she could not seek a chemical abortion because it was contraindicated due to the medications; yet the woman left the hospital and sought an abortion at Planned Parenthood of Indiana. The woman was given mifepristone by the doctor at Planned Parenthood and took the drug. The woman called an Uber for a ride home from Planned Parenthood. The woman began to experience bleeding and other adverse effects from the mifepristone. The woman's Uber driver did not take her home because she was so ill and instead brought her to the hospital's emergency department. At the hospital, the woman came under my care. The woman had not yet taken the second abortion drug, misoprostol. I treated the patient for the adverse effects she suffered and told her not to take the misoprostol given to her by Planned Parenthood because of the grave risk that she could bleed out and die.

PI App. 216–17. Another doctor recounted an experience where he treated a patient—who "suffered from two weeks of moderate to heavy bleeding, and then developed a uterine infection"—by providing her "with intravenous antibiotics" and performing a D&C procedure. PI App. 886. If the patient waited a few more days to go to the hospital, the doctor predicted that "she could have been septic and died." PI App. 886. Another doctor testified that he has encountered "at least a dozen cases of life-threatening complications" from these drugs, and the frequency of these emergency situations has only increased over time. PI App. 865.

The risks are only exacerbated for women who have ectopic pregnancies. PI App. 207. This occurs in approximately two percent of pregnancies. PI App. 539. As one doctor explained:

> Chemical abortion drugs will not effectually end an ectopic pregnancy because they exert their effects on the uterus, which leaves women at risk of severe harm from hemorrhage due to tubal rupture, in need of emergent surgery or potentially at risk

> of death. Failure to perform an ultrasound prior to prescribing abortion drugs will cause some women to remain undiagnosed and at high risk for these adverse outcomes.

PI App. 208. The risks are greater under FDA's relaxed standards. That is because "without an in-person examination, it is impossible to rule out an ectopic pregnancy," placing a woman "at an increased risk of rupture or even death." PI App. 886.

The doctors also face an injury from the irreconcilable choice between performing their jobs and abiding by their consciences. These doctors structured their careers so they would not have to administer abortions. And yet, because women often come to hospitals when they experience complications from these drugs, these doctors sometimes have no other choice but to perform surgical abortions. As one doctor testified:

> The FDA's expansion of chemical abortions also harms my conscience rights because it could force me to have to surgically finish an incomplete elective chemical abortion. I object to abortion because it ends a human life. My moral and ethical obligation to my patients is to promote human life and health. But the FDA's actions may force me to end the life of a human being in the womb for no medical reason.

PI App. 209–10. And this harm is not speculative. Several doctors confirmed that they have had to surgically complete an abortion or remove an unborn child. PI App. 886, 205. As one doctor testified: "In my practice, I have cared for at least a dozen women who have required surgery to remove retained pregnancy tissue after a chemical abortion. Sometimes this includes the embryo or fetus, and sometimes it is placental tissue that has not been completely expelled." PI App. 205. That same doctor described how she had to "perform[] a suction aspiration procedure" on one patient who took the pill but needed surgery to complete the abortion. PI App. 206. Others have seen it firsthand. One doctor recounted a time where a woman came to the

emergency room "with heavy vaginal bleeding and unstable vital signs as a result of taking chemical abortion drugs." PI App. 195. When the woman arrived in the emergency room, the baby in her womb was not dead; the doctors were "able to detect a fetal heartbeat." PI App. 195. But due to the mother's unstable condition, the doctors "had no choice but to perform an emergency D&C." PI App. 196. The doctor testified that her colleague "felt as though she was forced to participate in something that she did not want to be a part of—completing the abortion." PI App. 196.

And not only have these doctors suffered injuries in the past, but it's also inevitable that at least one doctor in one of these associations will face a harm in the future. *Cf. City of Los Angeles v. Lyons*, 461 U.S. 95 (1983). Here, the plaintiff-doctors have "'set forth' by affidavit or other evidence 'specific facts'" that they are certain to see more patients. *Clapper*, 568 U.S. at 411 (quoting *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 561 (1992)). That's because FDA has removed almost all of mifepristone's REMS and thus enabled women to (1) get the drug without *ever* talking to a physician, (2) take the drug without *ever* having a physical exam to ensure gestational age and/or an ectopic pregnancy, and (3) attempt to complete the chemical abortion regimen at home; FDA has also (4) directed the hundreds of thousands of women who have complications to seek "emergency care" from the plaintiffs and plaintiffs' hospitals. Several doctors testified that they have seen an increasing number of women coming to the emergency room with complications from chemical abortions due to FDA's virtual elimination of controls on the dispensing and administration of the drugs. PI App. 194, 205, 215, 866. And given how many women these doctors have seen in emergency departments in the past, these doctors quite reasonably know with statistical certainty—again, a statistic estimated on Mifeprex's own "Patient Agreement Form"—that women will continue needing plaintiffs' "emergency care." *See* PI App. 205, 215, 868. The crisis is "concededly

ongoing." *Friends of the Earth*, 528 U.S. at 184. Accordingly, plaintiffs face a "substantial risk" of recurrence. *Susan B. Anthony List v. Driehaus*, 573 U.S. 149, 158 (2014) (quotation omitted).

And even if one of the named doctors never sees another patient, it's inevitable that one of the thousands of doctors in plaintiff associations will. For example, one of the plaintiff associations, the American Association of Pro-Life Obstetricians & Gynecologists, "is the largest organization of pro-life obstetricians and gynecologists" and has "more than 7,000 medical professionals nationwide." PI App. 165. The Christian Medical and Dental Association has "more than 600 physicians and approximately 35 OBGYNs." PI App. 179. The American College of Pediatricians has a membership of "more than 600 physicians and other healthcare professionals." PI App. 187. These associations presented affidavits from individual members, elucidating the various harms discussed herein. *See Friends of the Earth*, 528 U.S. at 183–84. Thus, they have associational standing to sue on behalf of their members. *See N.Y. State Club Ass'n, Inc. v. City of New York*, 487 U.S. 1, 9 (1988); *Hunt v. Wash. State Apple Advertising Comm'n*, 432 U.S. 333, 343 (1977). That means that so long as one doctor among the thousands of members in these associations faces an injury, Article III is satisfied. *See Rumsfeld*, 547 U.S. at 52 n.2.

The doctors can also show that these injuries are traceable to FDA regulations and redressable by this court. *See Defs. of Wildlife*, 504 U.S. at 560–61. That's because the 2016 Major REMS Changes, the 2021 Petition Denial, and the 2023 Mail-Order Decision all empower *non-doctors* to prescribe mifepristone and thus shift the costs of the drug onto the plaintiff physicians who must manage the aftermath. *See, e.g.*, PI App. 218 ("I spent a significant amount of time that day working to save her life from unnecessary complications due to the irresponsible administration and use of mifepristone and misoprostol. As a result of the significant time that I devoted to that

patient, my time and attention was taken away from other patients, who also need my care."); PI App. 867 ("Because more women [who take mifepristone] are unnecessarily presenting in the emergency department, more of my time and attention is taken away from other patients who need it."). In this way, "[t]he FDA's actions have created a culture of chaos for emergency room physicians." PI App. 867. And we're capable of redressing plaintiffs' injuries by restoring the 2000 Approval's REMS. Accordingly, at this stage, applicants have not shown that all of the plaintiffs lack standing.

We hasten to emphasize the narrowness of this holding. We do not hold that doctors necessarily have standing to raise their patients' claims. *See supra* n.4. We do not hold that doctors have constitutional standing whenever they're called upon to do their jobs. And we do not hold that doctors have standing to challenge FDA's actions whenever the doctor sees a patient experiencing complications from an FDA-approved drug. Rather, we hold that on the record before us applicants know that hundreds of thousands of women *will*—with applicants' own statistical certainty—need emergency care on account of applicants' actions. And because applicants chose to cut out doctors from the prescription and administration of mifepristone, plaintiff doctors and their associations will necessarily be injured by the consequences. This is an exceedingly unusual regime. In fact, as far as the record before us reveals, FDA has not structured the distribution of any comparable drug in this way.

FDA's principal contention to the contrary is that mifepristone is comparable to "ibuprofen." FDA Stay App. 1. The theory appears to be that we cannot recognize plaintiffs' standing here without opening a pandora's box in which doctors have standing to litigate everything at all times, including the banalities of over-the-counter Advil.

We disagree because FDA's own documents show that mifepristone bears no resemblance to ibuprofen. In the 2000 Approval, FDA imposed a "Black Box" warning on mifepristone. FDA requires "Black Box" warnings when a drug "may lead to death or serious injury." 21 C.F.R. § 201.57(c)(1). In its 2000 Approval, FDA conditioned its approval of mifepristone on the inclusion of this "Black Box" warning:

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

FDA Add. 182. The 2016 Major REMS Changes relaxed many of the requirements for marketing and using mifepristone. But it retained this "Black Box" warning:

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

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

- **Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis *[see Warnings and Precautions (5.1)]*.**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding *[see Warnings and Precautions (5.2)]*.**

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MIFEPREX REMS Program *[see Warnings and Precautions (5.3)]*.

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

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

https://perma.cc/R56J-BHW4.

Ibuprofen's label, which FDA helpfully provided in its stay addendum, obviously bears no resemblance to the "Black Box" warning on mifepristone's label. FDA Add. 465–68. To the contrary, FDA has a special regulation regarding ibuprofen so all manufacturers of that over-the-counter medicine include the same information on their labels. *See* 21 C.F.R. § 201.326. It says nothing about REMS, surgery, emergencies, Emergency Rooms, or death.

In sum, applicants' own documents—from the "Patient Agreement Form" to the "Black Box" warning that have accompanied mifepristone

ever since the 2000 Approval up to and including today—prove that emergency room care is statistically certain in hundreds of thousands of cases. Plaintiff doctors have provided that emergency room care and are statistically certain to provide it in the future.

2.

Second, the associations have standing. As previously discussed, they have associational standing to sue on behalf of their members. *See N.Y. State Club Ass'n, Inc.*, 487 U.S. at 9; *Hunt*, 432 U.S. at 343. The associations presented affidavits from individual member doctors who have suffered harms. *See Friends of the Earth*, 528 U.S. at 183–84. Accordingly, they have standing to sue on their members' behalf.

Plaintiff associations have also suffered independent injuries because FDA's actions have frustrated their organizational efforts to educate their members and the public on the effects of mifepristone. *See Havens Realty Corp. v. Coleman*, 455 U.S. 363, 379 (1982) (holding that housing non-profit had standing to challenge racial steering practices that impaired its ability "to provide counseling and referral services for low-and-moderate-income homeseekers"). As a result, plaintiff associations have expended "time, energy, and resources to compensate for this lack of information by conducting their own studies and analyses of available data" to "the detriment of other advocacy and educational efforts." PI App. 174. The Supreme Court has previously stated that such a "concrete and demonstrable injury to the organization's activities—with the consequent drain on the organization's resources—constitutes far more than simply a setback to the organization's abstract social interests," *Havens*, 455 U.S. at 379, even where the organizational interest is purely "noneconomic," *id.* at 379 n.20. Rather, under these circumstances, "there can be no question that the organization has suffered an injury in fact." *Id.* at 379.

This injury is also traceable to FDA's elimination of non-fatal adverse events in the 2016 Major REMS Changes. And it's redressable by an order vacating those changes. Accordingly, these associations also have standing.

B.

Next we turn to timeliness.

Everyone acknowledges that 28 U.S.C. § 2401(a)'s six-year limitations period applies to all of this case's challenged actions. And plaintiffs' right of action against the lion's share of the challenged actions are squarely within the six-year window. That includes all of plaintiffs' alternative arguments challenging the 2016 Major REMS Changes, the 2019 Generic Approval, the 2021 Mail-Order Decision, and the 2021 Petition Denial of the 2019 Citizen Petition.

True, FDA's March 2016 Major REMS Changes were promulgated more than six years before plaintiffs filed suit in November 2022. But Section 2401(a) instructs that the six-year period begins when "the right of action first accrues." "And '[t]he right of action first accrues on the date of the final agency action.'" *Texas v. Biden*, 20 F.4th 928, 951 n.3 (5th Cir. 2021), *rev'd on other grounds*, 142 S. Ct. 2528 (2022) (quoting *Wash. All. of Tech. Workers v. DHS*, 892 F.3d 332, 342 (D.C. Cir. 2018)). Though FDA promulgated the Major REMS Changes in 2016, the Agency didn't respond to plaintiffs' 2019 Petition challenging those changes until December 16, 2021. So plaintiffs' right of action against FDA's final decision first accrued in December of 2021. *See* 21 C.F.R. § 10.45. That's less than a year before plaintiffs sued, which is well within the limitations period.

Next, applicants claim that plaintiffs' primary challenges to the 2000 Approval and FDA's 2016 Petition Denial to their 2002 Citizen Petition are time-barred. Though admittedly a close question, we ultimately agree with applicants at this preliminary juncture.

Plaintiffs' right of action against the 2000 Approval and 2016 Petition Denial first accrued on March 29, 2016—the date FDA issued its final decision rejecting their 2002 Petition challenging the 2000 Approval. *See* 21 C.F.R. § 10.45. But plaintiffs didn't file suit until November 18, 2022, more than six months beyond the statute of limitations. The district court nevertheless found timely the plaintiffs' challenges to the 2000 Approval and the 2016 Petition Denial. How? First, the district court held that FDA "reopened" those decisions in 2016 and 2021, thus restarting the statute of limitations. Second—and alternatively—the district court decided plaintiffs were entitled to equitable tolling.

We consider each justification in turn.

First, reopening. "The reopen[ing] doctrine allows an otherwise untimely challenge to proceed where an agency has—either explicitly or implicitly—undertaken to reexamine its former choice." *Nat'l Biodiesel Bd. v. EPA*, 843 F.3d 1010, 1017 (D.C. Cir. 2016) (quotation omitted). Put simply, the purpose of the reopening doctrine is "to pinpoint an agency's final action in cases where the agency has addressed the same issue multiple times." *Texas v. Biden*, 20 F.4th at 951. The limitations period runs from the agency's earlier decision unless the later decision "opened the issue up anew." *Ibid.* (quotation omitted). This makes good sense: Because a key step in the timeliness inquiry is determining when an agency action became final, it's sometimes necessary to determine whether an agency's subsequent action "actually reconsidered" its former action, *Growth Energy v. EPA*, 5 F.4th 1, 21 (D.C. Cir. 2021) (per curiam) (quotation omitted), or merely "reaffirm[ed] its prior position," *Sierra Club v. EPA*, 551 F.3d 1019, 1024 (D.C. Cir. 2008) (quotation omitted); *see also Texas v. Biden*, 20 F.4th at 951 ("If the agency opened the issue up anew, and then reexamined and reaffirmed its prior decision, the agency's second action (the reaffirmance) is reviewable. . . . But if the agency merely reaffirmed its decision without

really opening the decision back up and reconsidering it, the agency's initial action is the only final agency action to review." (quotation omitted)).

Courts have articulated various tests for determining whether an agency has reopened a prior decision. These tests fall into two general categories.

Under the first, courts look "to the entire context of the [relevant agency action] including all relevant proposals and reactions of the agency to determine whether an issue was in fact reopened." *Pub. Citizen v. Nuclear Regul. Comm'n*, 901 F.2d 147, 150 (D.C. Cir. 1990); *see also, e.g.*, *id.* at 150–53; *Growth Energy*, 5 F.4th at 21–22; *Nat'l Ass'n of Reversionary Prop. Owners v. Surface Transp. Bd.*, 158 F.3d 135, 141–46 (D.C. Cir. 1998). An agency can reopen an earlier decision in many ways, but the quintessential example of this type of reopening is when an agency "hold[s] out [its prior rule] as a proposed regulation, offer[s] an explanation for its language, solicit[s] comments on its substance, and respond[s] to the comments in promulgating the regulation in its final form." *Am. Iron & Steel Inst. v. EPA*, 886 F.2d 390, 397 (D.C. Cir. 1989). Under the second reopening category, courts consider whether an agency "constructively reopened" its prior decision. *Kennecott Utah Copper Corp. v. DOI*, 88 F.3d 1191, 1214–15 (D.C. Cir. 1996). They do so by evaluating whether "the revision of accompanying regulations significantly alters the stakes of judicial review as the result of a change that could have not been reasonably anticipated." *NRDC v. EPA*, 571 F.3d 1245, 1266 (D.C. Cir. 2009) (quotation omitted).

Although a close call, we are unsure at this preliminary juncture and after truncated review that FDA reopened the 2000 Approval in its 2016 Major REMS Changes and its 2021 Petition Denial.

As for the first reopening test, neither the 2016 Major REMS Changes nor the 2021 Petition Denial appears to "substantive[ly] reconsider[]"

FDA's 2000 Approval. *Growth Energy*, 5 F.4th at 21. FDA's 2016 decision to relax many of the REMS was issued in response to Danco's supplemental application requesting as much. *See* PI App. 615–52. And FDA's 2021 Petition Denial was issued in response to plaintiffs' 2019 Citizen Petition asking FDA to "restore" the pre-2016 REMS—not revoke or reconsider FDA's underlying 2000 Approval. *See* PI App. 667–93. Therefore neither of the "relevant proposals" prompted FDA to reopen and reconsider its 2000 Approval. *Pub. Citizen*, 901 F.2d at 150.

That said, the district court correctly noted that FDA nevertheless "undertook a full review of the Mifepristone REMS Program" when it reviewed plaintiffs' 2019 Citizen Petition—even though the plaintiffs only asked FDA to restore the pre-2016 status quo ante. *See* PI App. 735–76; FDA Add. 22. In FDA's words:

> In 2021, FDA also undertook a full review of the Mifepristone REMS Program. In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA[.]

PI App. 735. And after conducting this unrequested "full review" of the REMS Program, FDA (*inter alia*) added two modifications to the REMS Program that plaintiffs never even mentioned in their 2019 Citizen Petition, including "a requirement that pharmacies that dispense the drug be specially certified." PI App. 736; *see also id.* at 735 n.11 (acknowledging that "this was not raised in your Petition"). All of this suggests FDA went back to the beginning, including its very first REMS report, and conducted an

independent review that far exceeded the issues raised in the 2019 Citizen Petition.

Especially because the dangerousness of a drug is grounds to withdraw its approval, *see* 21 U.S.C. § 355(e)—and REMS are required to "ensure that the benefits of the drug outweigh the risks," *id.* § 355-1(a)(1)–(2)—plaintiffs reasonably argue that FDA's 2021 "full review" of the entire REMS Program was in effect a reconsideration of FDA's 2000 Approval. Indeed, plaintiffs might very well prevail on that claim later in this litigation. But at this early juncture—and in light of our necessarily truncated review—we are not yet confident enough to say that viewed in "the entire context," FDA "has undertaken a serious, substantive reconsideration of the [2000 Approval]" rather than "incremental adjustments to existing regulations." *Texas v. Biden*, 20 F.4th at 952–93 (quotation omitted).

The result is the same under the second reopening test. Recall that under the second test, "[a] constructive reopening occurs if the revision of accompanying regulations significantly alters the stakes of judicial review as the result of a change that could have not been reasonably anticipated." *Sierra Club*, 551 F.3d at 1025 (quotation omitted).

Sierra Club is the seminal case. In 1994, EPA adopted a rule that exempted major sources of air pollution from the Clean Air Act's emission standards during startups, shutdowns, and malfunctions (the "SSM exemption"). *Id.* at 1022. But the 1994 rule also required sources to develop an SSM plan in order to receive the benefit of the SSM exemption. *Ibid.* An SSM plan required "the source to demonstrate how it will do its reasonable best to maintain compliance with the standards, even during SSMs." *Ibid.* (quotation omitted). SSM plans were publicly available and were incorporated into the sources' permits under Title V of the Clean Air Act. *Ibid.*

In a series of rulemakings between 2002 and 2006, EPA substantially weakened the requirement that sources maintain and follow an SSM plan in order to benefit from the SSM exemption. It removed the requirement that a source's Title V permit incorporate its SSM plan; it stopped making SSM plans publicly available; and it ultimately retracted the requirement that sources implement their SSM plans during SSM periods. *Id.* at 1023.

The Sierra Club filed suit in 2007. But the Sierra Club did not challenge the changes to the SSM plan requirements that EPA had adopted in its 2002, 2003, and 2006 rulemakings. Instead, it challenged the legality of the SSM exemption itself. *Id.* at 1024. EPA had adopted that exception in 1994 and had not considered rescinding it in any of its rulemakings during the 2000s. Rather, those rulemakings had treated the SSM exemption as a given—in fact, they had strengthened it by weakening the SSM plan requirements. *See id.* at 1022–23.

The D.C. Circuit nonetheless held that the Sierra Club's challenge to the SSM exemption was timely. Even though EPA had not expressly reopened its decision to create a SSM exemption, it had constructively reopened that decision "by stripping out virtually all of the SSM plan requirements that it created to contain that exemption." *Id.* at 1025 (quotation omitted). Because EPA had allegedly abandoned these "necessary safeguards" limiting the SSM exemption, its rulemakings had "changed the calculus for petitioners in seeking judicial review and thereby constructively reopened consideration of the exemption." *Id.* at 1025–26 (quotation omitted).

Sierra Club thus establishes that an agency can constructively reopen a decision if it removes essential safeguards that had previously limited or contained the impact of that decision. In making this determination, the D.C. Circuit looks to the extent to which the agency has "alter[ed] th[e] regulatory

framework" and whether the agency has "work[ed] a change that [plaintiffs] could not have reasonably anticipated." *Nat'l Biodiesel Bd.*, 843 F.3d at 1017.

Under *Sierra Club* and its progeny, FDA's 2016 Major REMS Changes and 2021 Petition Denial seemingly reopened its 2000 Approval decision. Of course, FDA did not expressly reconsider its mifepristone approval. But it eliminated the "necessary safeguards," *Sierra Club*, 551 F.3d at 1025, that had accompanied and limited the impact of that approval for two decades. The in-person dispensing requirement, for example, was critical to FDA's initial approval of mifepristone in 2000, which relied on the in-person dispensing requirement to dismiss concerns about provider qualifications, improper use, illicit distribution, and detection of adverse events. *See* PI App. 519–23. And the in-person dispensing requirement was also the cornerstone of the REMS for mifepristone that FDA approved in 2011 and then relied on in its 2016 rejection of plaintiffs' 2002 Citizen Petition. *See* PI App. 578–82, 605, 608.

Thus FDA's elimination of the in-person distribution requirement—not to mention various other REMS—arguably worked a "sea change" in the legal framework governing mifepristone distribution that plaintiffs "could not have reasonably anticipated" and that "significantly alters the stakes of judicial review." *Nat'l Biodiesel Bd.*, 843 F.3d at 1017 (quotation omitted). That's because the in-person dispensing requirement was FDA's primary tool for ensuring the safe distribution and use of mifepristone, so plaintiffs arguably had little reason to anticipate this important change before 2021. FDA does not argue otherwise, appearing to concede that its 2021 announcement was a stark departure from previous regulatory approaches. And because this change eliminates a major safeguard against complications and adverse effects arising from improper mifepristone use, it can be said to "significantly alter[] the stakes of judicial review" for plaintiff doctors who treat patients with these complications. *Ibid.* (quotation omitted).

Even so, we ultimately hold at this early and emergency stage that these alterations didn't constructively reopen the 2000 Approval for review. That's because there's at least a colorable argument that plaintiffs "could have . . . reasonably anticipated" changes like those in 2016 and 2021 by dint of the statutorily defined supplemental application process and other similar revision mechanisms. *NRDC v. EPA*, 571 F.3d at 1266 (quotation omitted); *see, e.g.*, 21 C.F.R. § 314.71(b). We also recognize that it's somewhat of a strain to say that the 2016 Major REMS Changes and 2021 Petition Denial (and related changes) altered the regulatory landscape to such a degree that the prior rule is only now "worth challenging" when it otherwise might "not have been." *Sierra Club*, 551 F.3d at 1025–26 (quotation omitted). After all, plaintiffs *did* challenge the 2000 Approval well before the 2016 and 2021 changes were even proposed. But again, plaintiffs could very well prevail on this reopening claim.

In the alternative, the district court held that plaintiffs were entitled to equitable tolling of the statute of limitations. FDA Add. 23–25. We are unpersuaded. "[A] litigant is entitled to equitable tolling of a statute of limitations only if the litigant establishes two elements: '(1) that he has been pursuing his rights diligently, and (2) that some extraordinary circumstance stood in his way and prevented timely filing.'" *Menominee Indian Tribe of Wis. v. United States*, 577 U.S. 250, 255 (2016) (quoting *Holland v. Florida*, 560 U.S. 631, 649 (2010)). Here, no "extraordinary circumstance" prevented plaintiffs from filing within six years of FDA's 2016 Petition Denial. The district court is of course correct that FDA took "13 years, 7 months, and 9 days" to render that March 2016 ruling, FDA Add. 24, but that delay had no impact on the length of the statute-of-limitations period or plaintiffs' capacity to challenge the 2016 Petition Denial.

C.

Next exhaustion. Stay applicants contend they are likely to succeed on the merits because plaintiffs failed to exhaust their claims before FDA. We disagree.

"As a general rule, claims not presented to the agency may not be made for the first time to a reviewing court." *Wash. Ass'n for Television & Child. v. FCC*, 712 F.2d 677, 680 (D.C. Cir. 1983); *cf. United States v. L.A. Tucker Truck Lines*, 344 U.S. 33, 37 (1952). For challenges to FDA actions, the general administrative exhaustion requirement is codified at 21 C.F.R. § 10.45(b). Section 10.45(b) states that a "request that the [FDA] Commissioner take or refrain from taking any form of administrative action must first be the subject of a final administrative decision based on a petition submitted under § 10.25(a)." *See id.* § 10.25(a) ("An interested person may petition the [FDA] Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action.").

No one disputes that every argument the plaintiffs raised in their 2019 Citizen Petition is exhausted. That includes all of plaintiffs' challenges to the 2016 Major REMS Changes and everything fairly embraced by those challenges. For example, the 2019 Citizen Petition argued explicitly that FDA should "[c]ontinue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals." FDA Add. 193, 209–16. When FDA rejected that request in the 2021 Petition Denial, it expressly reaffirmed its commitment to mail-order abortion drugs. As such, plaintiffs have properly exhausted their challenge to FDA's by-mail distribution regime by raising it in the 2019 Citizen Petition.

Even if plaintiffs failed to exhaust their claims, courts retain "discretion to waive exhaustion" where one of the "traditionally

recognized" exceptions applies. *Wash. Ass'n for Television & Child.*, 712 F.2d at 681–82. Two exceptions are relevant here: futility and administrative abuse of process.

Start with futility. Plaintiffs need not exhaust claims where they can demonstrate "the futility or inadequacy of administrative review." *Gardner v. Sch. Bd. Caddo. Par.*, 958 F.2d 108, 112 (5th Cir. 1992); *see also Honig v. Doe*, 484 U.S. 305, 327 (1988). The futility exception applies when exhaustion would be "clearly useless" and "it is certain [a] claim will be denied." *Tesoro Refin. & Mktg. Co. v. FERC*, 552 F.3d 868, 874 (D.C. Cir. 2009) (quotation omitted); *see also Carr v. Saul*, 141 S. Ct. 1352, 1361 (2021) ("[T]his Court has consistently recognized a futility exception to exhaustion requirements.").

Given FDA's 2016 Petition Denial and its 2021 Petition Denial, it would have been futile for plaintiffs to include a challenge to the 2000 Approval in their 2019 Citizen Petition. FDA rejected this exact challenge in its 2016 Petition Denial. So it would have been "clearly useless" to raise the precise challenge again in the 2019 Citizen Petition. Further, this exact reasoning applies with equal force to plaintiffs' challenge to the 2019 Generic Approval because it's entirely dependent on the underlying 2000 Approval. Thus, plaintiffs' challenges to the 2000 Approval and the 2019 Generic Approval are not barred by exhaustion.

Next, administrative abuse of process. It's well-established that where an agency fails to follow its own regulations, exhaustion may not be required. *See Way of Life Television Network, Inc. v. FCC*, 593 F.2d 1356, 1359–60 (D.C. Cir. 1979); *see also Wash. Ass'n for Television & Child.*, 712 F.2d at 681. That's especially true "where the obvious result would be a plain miscarriage of justice." *Hormel v. Helvering*, 312 U.S. 552, 558 (1941). Here, FDA was required by its own regulations to respond to citizen petitions within 180

days. *See* 21 C.F.R. § 10.30(e)(2). Instead of timely responding, FDA responded to plaintiffs' first petition fourteen years after it was filed. And it responded to the second petition over two years after it was filed. FDA plainly and repeatedly refused to follow its own regulations here. Even assuming any of plaintiffs' challenges were unexhausted and that it wasn't futile to raise them before FDA, FDA's repeated failure to follow its own regulations indicates that the district court did not abuse its "discretion to waive exhaustion." *Wash. Ass'n for Television & Child.*, 712 F.2d at 681.

D.

As applicants recognize, FDA's actions are constrained by the APA's arbitrary-and-capricious standard. *See* 5 U.S.C. § 706(2)(A). Under that standard, "the agency must examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (quotation omitted); *see also Sw. Elec. Power Co. v. EPA*, 920 F.3d 999, 1013 (5th Cir. 2019) (judicial review of agency action "is not toothless"). We must "consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *State Farm*, 463 U.S. at 43 (quotation omitted). An agency's action is "arbitrary and capricious" if it "entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Ibid.*

When an agency acts, it must "reasonably consider[] the relevant issues and reasonably explain[]" its actions. *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021); *see also ibid.* ("The APA's arbitrary-and-capricious standard requires that agency action be reasonable and reasonably

explained."); *Michigan v. EPA*, 576 U.S. 743, 750, 752 (2015) ("[A]gency action is lawful only if it rests on a consideration of the relevant factors" and "important aspect[s] of the problem." (quotation omitted)). Of course, we cannot "substitute" our "own policy judgment for that of the agency." *Prometheus*, 141 S. Ct. at 1158. We nonetheless must still carefully ensure that "the agency has acted within a zone of reasonableness and, in particular, has reasonably considered the relevant issues and reasonably explained the decision." *Ibid.* The upshot is that we "must set aside any action premised on reasoning that fails to account for 'relevant factors' or evinces 'a clear error of judgment.'" *Univ. of Tex. M.D. Anderson Cancer Ctr. v. HHS*, 985 F.3d 472, 475 (5th Cir. 2021) (quoting *Marsh v. Or. Nat. Res. Council*, 490 U.S. 360, 378 (1989)).

Here, applicants have failed to carry their burden at this preliminary stage to show that FDA's actions[5] were not arbitrary and capricious. We have two principal concerns in that regard. First, FDA failed to "examine the relevant data" when it made the 2016 Major REMS changes. *State Farm*, 463 U.S. at 43. That's because FDA eliminated REMS safeguards based on studies that *included those very safeguards.* FDA Add. 59, 122–23, 171. Imagine that an agency compiles studies about how cars perform when they have passive restraint systems, like automatic seatbelts. *See State Farm*, 463 U.S. at 34–36. For nearly a decade, the agency collects those studies and continues studying how cars perform with passive safety measures. Then one day the agency changes its mind and *eliminates* passive safety measures based only on existing data of how cars perform *with* passive safety measures. *Cf. id.* at 47–

[5] Here we limit our discussion to FDA's decisions in the 2016 Major REMS Changes and its subsequent agency actions. As described above in Part III.B, it appears at this preliminary juncture that plaintiffs' challenges to the 2000 Approval and 2016 Petition Denial are untimely.

49. That was obviously arbitrary and capricious in *State Farm*. And so too here. The fact that mifepristone might be safe when used with the 2000 Approval's REMS (a question studied by FDA) says nothing about whether FDA can eliminate those REMS (a question not studied by FDA).

True, FDA studied the safety consequences of eliminating one or two of the 2000 Approval's REMS in *isolation*. But it relied on zero studies that evaluated the safety-and-effectiveness consequences of the 2016 Major REMS Changes *as a whole*. This deficiency shows that FDA failed to consider "an important aspect of the problem" when it made the 2016 Major REMS Changes. *Michigan v. EPA*, 576 U.S. at 752 (quotation omitted).

Second, the 2016 Major REMS Changes eliminated the requirement that non-fatal adverse events must be reported to FDA. After eliminating that adverse-event reporting requirement, FDA turned around in 2021 and declared the absence of non-fatal adverse-event reports means mifepristone is "safe." *See, e.g.*, FDA Add. 861–76 (explaining that FDA's FAERS database, which collates data on adverse events, indicated that the 2016 Major REMS Changes hadn't raised "any new safety concerns"). This ostrich's-head-in-the-sand approach is deeply troubling—especially on a record that, according to applicants' own documents, necessitates a REMS program, a "Patient Agreement Form," and a "Black Box" warning. *See supra* Part III.A. And it suggests FDA's actions are well "outside the zone of reasonableness." *Prometheus*, 141 S. Ct. at 1160. It's unreasonable for an agency to eliminate a reporting requirement for a thing and then use the resulting absence of data to support its decision.

These actions make it unlikely that plaintiffs' arbitrary-and-capricious challenges will fail on the merits, at least as far as they challenge FDA's decisions including and following the 2016 Major REMS Changes.

IV.

Beyond likelihood of success on the merits, we also must consider the other three factors for granting a stay. Those are "[A] whether the applicant will be irreparably injured absent a stay; [B] whether issuance of the stay will substantially injure the other parties interested in the proceeding; and [C] where the public interest lies." *Nken*, 556 U.S. at 434 (quotation omitted). We address each in turn. And we (D) discuss how the Comstock Act, 18 U.S.C. §§ 1461, 1462 affects the stay inquiry. Outside of the 2000 Approval, we find that the applicants fail to make a strong showing on any of these factors for a stay.

A.

Of the remaining three factors, irreparable injury matters most. *See Nken*, 556 U.S. at 434. FDA argues that the plaintiffs fail to show irreparable injury. But the irreparable injury factor asks whether "*the [stay] applicant* will be irreparably injured" absent a stay, not whether the plaintiff would be irreparably injured absent an injunction. *Ibid.* (emphasis added) (quotation omitted). Similarly, FDA's assertion that the district court's injunction will harm pregnant women or other members of the public does not speak to the irreparable injury factor (although it may speak to other factors), because those persons are not stay applicants in this case.

Since FDA does not articulate any irreparable harm that *FDA* will suffer absent a stay, it makes no showing on this "critical" prong. *Ibid.* We may not need to address the merits of the applicants' stay request any further, because failure to show irreparable injury often "decides the [stay] application." *Whalen v. Roe*, 423 U.S. 1313, 1318 (1975) (Marshall, J., in chambers).

Danco by contrast does claim it will suffer irreparable injury, albeit in just one paragraph. Danco notes that mifepristone is its sole product and

argues that it may have to shut down absent relief. We have held that catastrophic financial losses "*may* be sufficient to show irreparable injury." *Wages & White Lion Investments, LLC v. FDA*, 16 F.4th 1130, 1142 (5th Cir. 2021) (emphasis added) (quotation omitted). Of course, irreparable injury alone does not entitle Danco to a stay. *See Virginian Ry. Co.*, 272 U.S. at 672.

And even if it did, neither FDA nor Danco articulates why this, or any other, injury would require a stay of *all* of the district court's order, rather than only part. Recall that we may narrowly "tailor a stay" to impact "only some portion of the proceeding." *Int'l Refugee Assistance Project*, 137 S. Ct. at 2087 (quotation omitted). The applicants' arguments suggest, at best, that they require relief only from the district court's treatment of the 2000 Approval. They make no argument as to why the district court's treatment of the 2016 Major REMS Changes and later FDA activity irreparably harms anyone.

Applicants' forfeiture of this contention is understandable because the world operated under the 2000 Approval for sixteen years, apparently without problems. And neither applicant contends that it'll be irreparably injured without a stay so long as the 2000 Approval and its associated REMS remain in effect. Thus, the irreparable injury factor counsels against a stay.

B.

The next *Nken* factor asks whether "issuance of the stay will substantially injure the other parties interested in the proceeding." 556 U.S. at 434 (quoting *Hilton*, 481 U.S. at 776); *see also Ala. Ass'n of Realtors*, 141 S. Ct. at 2487 (same); *Planned Parenthood v. Abbott*, 134 S. Ct. 506, 506–08 (2013) (mem.) (opinions of seven Justices using the same standard). This language again focuses on harm from the *stay*, not the injunction. *Cf. Whole Woman's Health*, 141 S. Ct. at 2495 (using less specific "balance of the equities" language). To succeed on this prong, applicants must show that the

requested stay will not harm the opposing appellees or other interested parties.

Applicants discuss at length their view that *the district court's order* might harm various persons, but mostly decline to address the apposite question, which is why *the requested stay* would not harm relevant persons. What points the applicants do make on this relevant question distill down to two arguments.

First, applicants briefly argue that the injuries the plaintiffs would suffer from a stay are speculative or minimal. But we have already addressed why plaintiffs' injuries are non-speculative. *See supra* Part III.A. We have also addressed the specific risks impacting women and the plaintiffs that stem from the 2016 Major REMS Changes and other post-2016 FDA decisions that the district court enjoined. *See supra* Part III.A, D. The applicants' abbreviated argument focuses on consequences flowing from the district court's treatment of the 2000 Approval and largely ignores plaintiffs' alternative arguments regarding the 2016 Major REMS Changes and what followed.

Second, the applicants argue that the plaintiffs' failure to bring litigation sooner undercuts any contention that they would be harmed from a stay. That contention is untenable given FDA's *fourteen-year delay* in adjudicating the 2002 Citizen Petition. But, even setting aside FDA's own delays, the applicants do not explain why the plaintiffs' alleged procrastination warrants a stay of the entirety of the district court's order, rather than just the portion of the order impacted by long litigation delay (the 2000 Approval).

To the extent applicants make any showing that the third *Nken* factor favors a stay, they do so only with respect to the 2000 Approval and do not address plaintiffs' alternative arguments.

C.

The last *Nken* factor asks "where the public interest lies." 556 U.S. at 434 (quotation omitted). The stay applicants make three principal arguments.

First, the applicants argue that "procedural irregularity" in the court below favors relief. But the applicants do not explain why any specific alleged irregularity necessarily speaks to public (versus their own private) interest. Even if we assume away that problem, it is not clear to us, on our accelerated review, that any litigation below was irregular. And even if we assume, which we do not, that the district court or the plaintiffs departed from acceptable procedure, it's unclear on this record that applicants have embraced "the principles of equity and righteous dealing" in the twenty-one years since the filing of the 2002 Citizen Petition. *Binh Hoa Le v. Exeter Fin. Corp.*, 990 F.3d 410, 416 (5th Cir. 2021) (quotation omitted) (noting that a party's own imperfect conduct can prejudice their request for equitable relief).

Second, Danco argues that avoidance of "judicial conflict" warrants a stay given the order of an out-of-circuit district court. Comity between federal courts is a cognizable interest. *See Def. Distrib. v. Platkin*, 55 F.4th 486, 495–96 (5th Cir. 2022). We have every respect for fellow federal courts. But we cannot embrace an argument that would, in effect, allow the decision of an out-of-circuit district court to impel us towards "extraordinary" relief that would be otherwise inappropriate. *Williams*, 442 U.S. at 1311 (quotation omitted).

Third, the stay applicants warn us of significant public consequences should the district court's order result in the withdrawal of mifepristone from the market. These consequences, the applicants say, include injury to pregnant women, to public healthcare systems, and to the sense of order that governs FDA drug approvals. But these concerns center on the district

court's removal of mifepristone from the market. The applicants make no arguments as to why the 2016 Major REMS Changes, the 2019 Generic Approval, or the 2021 and 2023 Mail Order Decisions are similarly critical to the public even though they were on notice of plaintiffs' alternative requests for relief. And it would be difficult for applicants to argue that the 2016 Major REMS Changes and subsequent FDA activity were so critical to the public given that the Nation operated—and mifepristone was administered to millions of women—without them for sixteen years following the 2000 Approval.

The applicants have made some showing that the public interest warrants equitable relief from the district court's treatment of the 2000 Approval. Motivated in part by the accelerated posture of our review, we credit their showing.

D.

The parties vehemently dispute how their competing interpretations of the Comstock Act of 1873 might impact the validity of the district court's order. The Comstock Act prohibits the carriage in interstate commerce of "any drug, medicine, article, or thing designed, adapted or intended for producing abortion." 18 U.S.C. § 1462. It similarly prohibits the mailing of any "article, instrument, substance, drug, medicine, or thing which is advertised or described in a manner calculated to lead another to use or apply it for producing abortion." *Id.* § 1461.

Both statutory provisions specify a *mens rea* of "knowingly." *Id.* §§ 1461–62. The plain text does not require that a user of the mails or common interstate carriage intend that an abortion actually occur. Rather, a user of those shipping channels violates the plain text merely by knowingly making use of the mail for a prohibited abortion item.

The applicants' principal defense against the Comstock Act is that FDA was not required to consider it. After all, say the applicants, 21 U.S.C. §§ 355 and 355-1 guide FDA's discretion over drug approval and REMS, and those statutes do not explicitly require consideration of other statutes like 14 U.S.C. § 1462.

Even assuming that's true, however, the Comstock Act nevertheless undermines applicants' showing on the final three *Nken* factors. For example, if the Comstock Act is construed in-line with its literal terms, then Danco cannot say it is irreparably harmed by the district court's order, because Danco has no interest in continuing to violate the law, which (under a plain view of the Act) it does every time it ships mifepristone. For further example, if the Comstock Act is strictly understood, then applicants may lose the public interest prong entirely, because there is no public interest in the perpetuation of illegality. *See Louisiana v. Biden*, 55 F.4th 1017, 1035 (5th Cir. 2022).

The applicants raise other defenses. For example, they argue that the Food and Drug Administration Amendments Act, Pub. L. No. 110-85, 121 Stat. 823 (2007) ("FDAAA") *sub silentio* repealed the Comstock Act, at least where mifepristone is concerned. That's because the FDAAA in 2007 created a statutory framework governing REMS and drugs with then-existing distribution restrictions. *See id.* § 909(b). Mifepristone was one such drug. So, say applicants, the FDAAA acted to legalize shipment of mifepristone, regardless of what the Comstock Act might say. But "repeals by implication are not favored." *Maine Cmty. Health Options v. United States*, 140 S. Ct. 1308, 1323 (2020) (quotation omitted). We regard each of Congress's statutes as effective unless either "intention to repeal" one of them is "clear and manifest" or the two laws are "irreconcilable." *Ibid.* (quotation omitted). Section 909(b) did not expressly legalize mifepristone; agency action (not statute) did that. Section 909(b)'s brief text makes no mention of

mifepristone at all. So, there is no "irreconcilable" conflict. And we hesitate to find "clear and manifest" intention to repeal a 150-year-old statute that Congress has otherwise repeatedly declined to alter in the far reaches of a single section of the cavernous FDAAA.

Failing all else, the applicants argue that the Comstock Act does not mean what it says it means. Or rather, that judicial gloss and lax enforcement over the past century act to graft relevant exceptions onto it. The applicants rely on a memo authored by the Office of Legal Counsel to press this position. *See* FDA Add. 258–78. That memo's thorough exploration of this topic notes that a variety of aging out-of-circuit opinions and a single footnote within one Supreme Court dissent favor the applicants' position. FDA Add. 262–68).

The speed of our review does not permit conclusive exploration of this topic. To the extent the Comstock Act introduces uncertainty into the ultimate merits of the case, that uncertainty favors the plaintiffs because the applicants bear the burden of winning a stay. *See Landis*, 299 U.S. at 255. Since plaintiffs already prevail on most *Nken* factors concerning most of the agency items effectively enjoined by the district court's order, we need not definitively interpret the Comstock Act to resolve this stay application.

* * *

As the stay applicants, defendants bear the burden of showing why "extraordinary circumstances" demand that we exercise discretion in their favor. To the extent the defendants make any such showing, they do so *only* with respect to the 2000 Approval—*not* the plaintiffs' alternative arguments challenging FDA's 2016 Major REMS Changes and all subsequent actions. Our decision to grant partial relief does not reflect our view on any merits question. The defendants' motions to stay the district court's order are GRANTED IN PART and DENIED IN PART. The appeal is EXPEDITED to the next available Oral Argument Calendar.