Nos. 23-235, 23-236

IN THE

Supreme Court of the United States

U.S. FOOD AND DRUG ADMINISTRATION, ET AL.,
Petitioners,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents,

DANCO LABORATORIES, L.L.C.,
Petitioner,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents.

On Writs of Certiorari to the United States Court of Appeals for the Fifth Circuit

BRIEF FOR DANCO LABORATORIES, LLC

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QUESTIONS PRESENTED

In 2000, the Food and Drug Administration (FDA) approved Danco's drug Mifeprex for termination of early pregnancy based on the agency's expert judgment that clinical data showed the drug to be safe and effective. The agency later modified certain conditions of use for mifepristone in 2016 and 2021, again relying on clinical data and the agency's expert judgment that the drug would remain safe and effective under the modified conditions of use. In 2022, associations of doctors who have never prescribed Mifeprex sued FDA, arguing that FDA's actions modifying the drug's conditions of use in 2016 and 2021 violated the Administrative Procedure Act. The questions presented are:

1. Whether an association can demonstrate Article III standing to enjoin a government action by arguing that some unspecified member may be injured at some future time by the challenged action; and

2. Whether the Fifth Circuit erred in upholding the preliminary injunction of FDA's 2016 and 2021 actions based on the court's review of an incomplete administrative record.

PARTIES TO THE PROCEEDING

Petitioners in this Court are Danco Laboratories, LLC, which was an intervenor-appellant below, and the U.S. FDA; Robert M. Califf, M.D., in his official capacity as Commissioner of Food and Drugs; Janet Woodcock, M.D., in her official capacity as Deputy Commissioner of Food and Drugs; Patrizia Cavazzoni, M.D., in her official capacity as Director of FDA's Center for Drug Evaluation and Research; the U.S. Department of Health and Human Services (HHS); and Xavier Becerra, in his official capacity as Secretary of HHS, which were defendants-appellants below.

Respondents were plaintiffs-appellees below. They are 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.; and George Delgado, M.D.

CORPORATE DISCLOSURE STATEMENT

Pursuant to Supreme Court Rule 29.6, Danco Laboratories, LLC hereby states that it is a wholly-owned subsidiary of Danco Investors Group, LP. No publicly held corporation owns 10% or more of the stock of either entity.

RELATED PROCEEDINGS

Supreme Court of the United States (U.S.):

- *Danco Laboratories, LLC* v. *Alliance for Hippocratic Medicine, et al.*, No. 22A901 (Apr. 21, 2023) (granting application for stay)
- *Food & Drug Administration, et al.* v. *Alliance for Hippocratic Medicine, et al.*, No. 22A902 (Apr. 21, 2023) (granting application for stay)
- *Alliance for Hippocratic Medicine, et al.* v. *Food & Drug Administration, et al.*, No. 23-395 (Dec. 13, 2023) (denying conditional cross-petition for certiorari)

United States Court of Appeals (5th Cir.):

- *Alliance for Hippocratic Medicine, et al.* v. *U.S. Food & Drug Administration et al.*, No. 23-10362 (Aug. 16, 2023) (partially affirming grant of preliminary injunction)
- *Alliance for Hippocratic Medicine, et al.* v. *U.S. Food & Drug Administration et al.*, No. 23-10362 (Apr. 12, 2023) (partially granting and partially denying stay pending appeal)

United States District Court (N.D. Tex.):

- *Alliance for Hippocratic Medicine, et al.* v. *U.S. Food & Drug Administration et al.*, No. 2:22-cv-223 (Apr. 7, 2023) (granting preliminary injunction)

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BRIEF FOR DANCO LABORATORIES, LLC

INTRODUCTION

Millions of women have safely and effectively used mifepristone in the nearly two and a half decades since FDA approved it for the termination of early pregnancy. Respondents are doctors and associations of doctors who do not prescribe mifepristone. They are opposed to all forms of abortion and would prefer if mifepristone were not available for other healthcare providers to prescribe. At their request, the Fifth Circuit upheld a preliminary injunction upending—years after the fact—FDA's 2016 and 2021 actions

relating to mifepristone's approved labeling and conditions of use. This injunction is unprecedented.

The questions presented are not hard under existing precedent. They do not ask the Court to wade into a politically charged debate around abortion. The same rules govern here that govern any challenge to agency action by any plaintiff. This Court's precedents therefore make short work of this case.

First, Respondents lack standing. The court of appeals held that Respondents established associational standing by showing that other healthcare providers prescribe mifepristone to women who might someday seek care in an emergency room where some member of a Respondent association might be asked to provide some sort of post-medication-abortion care. Respondents' speculative claims of injury to unknown association members based on attenuated chains of unknown third parties' actions and circumstances satisfy none of the Article III standing requirements.

Second, Respondents presented no valid basis to enjoin FDA's reasonable and reasonably explained decision to modify requirements related to mifepristone's use in 2016 and 2021. Although a court's deferential review of agency action requires evaluating "the whole record," 5 U.S.C. § 706, the Fifth Circuit rushed to enjoin FDA's actions without the entirety of the documents on which FDA based its decisions. Yet, even the subset of administrative-record documents before the court contained hundreds of pages of careful assessment of the scientific and data-driven basis for each of FDA's conclusions. Neither Respondents' disagreement with those conclusions, nor the lower courts' picayune

quarrels with FDA's exercise of predictive judgment, support entry of this unprecedented injunction.

The Fifth Circuit ran roughshod over this Court's precedents. Those errors have serious consequences. The court's standing analysis would give medical organizations standing to challenge virtually every government regulation that touches on health or safety. And its merits analysis threatens to destabilize the pharmaceutical industry, which relies both on FDA's ability to make predictive judgments and on courts not second-guessing those scientific judgments. PhRMA Cert. Br. 19-21; Pharm. Cos. Cert. Br. 20-22.

This Court should now reverse. These same analytical shortcomings and industry-wide repercussions were before the Court at the emergency stay stage, and this Court granted emergency stay relief. The Fifth Circuit merits panel then doubled down on the same injunction this Court had already stayed. Reversal will not foreclose FDA's continued real-world evaluation of the use restrictions "necessary to ensure that the benefits of the drug outweigh the risks of the drug," 21 U.S.C. § 355-1(a)(1)—the same standard FDA applies to every drug with use restrictions. Nor will it pass judgment on the validity of any individual State's laws addressing access to abortion care. It will simply ensure that the claims brought by these would-be litigants are assessed under the same standards this Court has consistently said govern federal jurisdiction and questions of administrative law. And under those standards, this case is straightforward to resolve in favor of Danco and the government.

OPINIONS BELOW

The Fifth Circuit's opinion is reported at 78 F.4th 210 (5th Cir. 2023). Pet. App. 1a-110a.[1] The District Court's memorandum opinion and order is reported at ___ F. Supp. 3d ___, and available at 2023 WL 2825871 (N.D. Tex. Apr. 7, 2023). Pet. App. 111a-195a.

JURISDICTION

The Fifth Circuit entered judgment on August 16, 2023. This Court has jurisdiction under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

Pertinent provisions are set out in FDA's Petition Appendix. *See* Pet. App. 249a-254a.

STATEMENT OF THE CASE

A. Statutory And Regulatory Background

The Food, Drug, and Cosmetic Act (FDCA) prohibits the "marketing [of] any drug in interstate commerce" absent FDA approval. *Mut. Pharm. Co.* v. *Bartlett*, 570 U.S. 472, 476 (2013) (citation omitted); *see* 21 U.S.C. §§ 355(a), 331(d). Once a new drug application (NDA) is filed, a team of "medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts * * * evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use." FDA, *FDA's Drug Review Process: Continued* (2015).[2]

Because "[f]ew if any drugs are completely safe in the sense that they may be taken by all persons in all

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[1] For consistency, citations are to FDA's Petition Appendix.

[2] https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-continued.

circumstances without risk," in this context, "safe" means that "the expected therapeutic gain justifies the risk entailed by its use." *United States* v. *Rutherford*, 442 U.S. 544, 555 (1979); *see* 21 U.S.C. § 355(d). If FDA determines "upon the basis of the information submitted" or otherwise "before" the agency that the drug is "safe for use" and there is "substantial evidence that the drug will have the effect it purports or is represented to have," FDA "shall" approve the drug. 21 U.S.C. § 355(d); *see* 21 C.F.R. § 314.105(c).

Once a drug is approved, a pharmaceutical manufacturer wishing to make dosing or other changes to the drug's labeling must typically submit a supplemental new drug application (sNDA) and obtain FDA's approval. 21 U.S.C. §§ 355(d), 356a; *see* 21 C.F.R. § 314.70. Applications proposing a new indication or change to the dosing regimen undergo the same rigorous review process as NDAs. *See* FDA Scholars Cert. Br. 3-4.

FDA may also impose certain use restrictions on drugs through its Risk Evaluation and Mitigation Strategy (REMS) authority if "necessary to ensure that the benefits of the drug outweigh" its risks. 21 U.S.C. § 355-1(a)(1). Under its REMS authority, FDA may (among other things) require prescribers, pharmacies, or health care settings that dispense the drug to be certified. *Id.* § 355-1(f)(3). Those restrictions can later be "modified" or "removed" if FDA determines they are no longer necessary to ensure the drug's benefits outweigh any risks. *Id.* § 355-1(g)(4).

B. Factual Background

Danco, a small pharmaceutical company incorporated in Delaware, holds the NDA for Mifeprex (mifepristone) Tablets for use in a regimen with misoprostol for the medical termination of intrauterine pregnancy.

FDA first approved Mifeprex in 2000. FDA imposed certain use restrictions with that approval, including that the drug be dispensed by a doctor in-person and that patients have an in-person follow-up appointment. Those use restrictions were deemed a REMS by the 2007 amendments to the FDCA. *See* 73 Fed. Reg. 16,313 (Mar. 27, 2008). The statute also required Danco to submit an sNDA for its REMS, which Danco did and which FDA approved in 2011. ROA 672-675.[3]

1. 2016 sNDA Approval And Labeling Changes

In 2015, Danco submitted an sNDA to modify certain aspects of Mifeprex's prescribing information and REMS. FDA approved these changes after considering dozens of studies reporting the outcomes for tens of thousands of women under various combinations of the proposed changes and 15 years of data reflecting the drug's safety profile.

i. Prescribing information: dosing and gestational age

FDA approved lowering the mifepristone dose from 600 to 200 milligrams (mg) and increasing the misoprostol dose from 400 to 800 micrograms (mcg), changing the misoprostol route of administration from

[3] References to "ROA" are to the Record on Appeal in the Fifth Circuit.

oral to buccal (in the cheek pouch), changing the dosing time interval between Mifeprex and misoprostol from 48 hours to 24-48 hours, and extending the approved gestational age from 49 to 70 days. FDA considered 22 studies of over 35,000 women supporting this new dosing regimen, J.A. 446-450, and seven studies of 934 women supporting increasing the gestational-age cutoff, many of which also used the proposed dosing regimen, J.A. 455-456.

FDA summarized these studies in the following tables, reflecting that "97.4% (US) and 96.1% (non-US)" of the patients required no further intervention. J.A. 449. These data showed "that the proposed new dosing regimen is considerably more effective for all gestations through 70 days"—meaning fewer women needed additional intervention such as a surgical abortion—as compared to the data supporting the initial approval through 49 days. J.A. 451.

Table 3: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later - US Studies

Study &Year	Design, Location	Gestation (maximum days)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Middleton 2005[24] US	Prospective	56	24-48	216	94.9
Winikoff 2008[23] US	Prospective	63	24-36	421	96.2
Fjerstad 2009[27] US	Retrospective	59	24-48	1,349	98.3
Grossman 2011[36] US - Clinic Mife v. Tele-med	Prospective	63	24-48	449	Clinic: 96.9% Telemed: 98.7%
Winikoff 2012[19] US	Prospective	57-70	24-48	629	93.2
Gatter 2015[13] US	Retrospective	63	24-48	13,373	97.7
Chong 2015[17] US	Prospective	63	24-48	357	96.7
TOTALS	**7 Studies**	**56-70 days**	**24-48 hr**	**16,794**	**97.4**

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

Table 4: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later- Non- US Studies

Study &Year/Country	Design, Location	Gestation (maximum)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Alam 2013[37] Bangladesh	Prospective	63	24	629	92.7
Blum 2012[70]	Prospective	63	24	210	92.9
Boersma 2011[22] Curacao	Prospective	70	24-48	307	97.7
Chai 2013[38] Hong Kong	Prospective	63	48	45	95.6
Dahiya 2012[39] India	Prospective	50	24	50	92
Chong 2012[40] Georgia, Vietnam	Prospective	63	36-48	560	96.4
Giri 2011[41] Nepal	Prospective	63	24	95	93.6
Goldstone 2012[20] Australia	Retrospective	63	24-48	11,155	96.5
Louie 2014[14] Azerbaijan	Prospective	63	24-48	863	97.3
Ngo 2012[42] China	Retrospective	63	36-48	167	91.0
Ngoc 2011[43] Vietnam	Prospective	63	24	201	96.5
Ngoc 2014[16] Vietnam	Prospective	63	24-48	1,371	94.7
Olavarietta 2015[85] Mexico	Prospective	70	24	884	98.2
Pena 2014[44] Mexico	Prospective	70	24-48	971	97.3
Sanhueza 2015[48] Mexico	Prospective	70	24-48	896	93.3
TOTALS	15 Studies	56-70 days	24-48 hrs	18,425	96.1%

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

J.A. 447-449 (emphases added).

FDA also analyzed the data and literature concerning serious adverse events for the proposed new dosing regimen and concluded it was "safe to approve through 70 days gestation." J.A. 475; *see* J.A. 469-475. The data showed that "[s]erious adverse events" were "exceedingly rare," "generally far below 1.0% for any individual [serious] adverse event." J.A. 474.

ii. Number of in-person clinical visits and prescribing providers

Before 2016, FDA required three in-person clinical visits: one to receive Mifeprex; one to receive misoprostol two days later; and one to follow up. After

analyzing numerous studies involving tens of thousands of women, FDA determined there was no safety or efficacy reason to mandate that the latter two visits be conducted in person.

In considering the change to allow at-home administration of misoprostol, FDA reviewed 11 studies involving 30,763 women who took misoprostol at home. J.A. 458. "The two largest studies * * * showed 97% success using the new proposed dosing regimen with home use of buccal misoprostol." J.A. 459. These studies also showed comparable results through 63 and 70 days gestation. J.A. 458. Based on this data, FDA concluded that at-home use of misoprostol is effective, J.A. 459, and "safe to approve," J.A. 479-481.

FDA also found that several studies, including one of over 45,000 women, supported allowing multiple methods of follow-up. J.A. 462. FDA explained that "[f]ollow-up after taking Mifeprex and misoprostol is necessary," but that "[t]he exact timing and method [of follow-up] should be flexible and determined jointly by the healthcare provider and the individual woman being treated." *Id.* FDA noted that there were several advantages to allowing alternative follow-up methods and that "no single option is superior to the others." *Id.*

FDA also approved changing the terminology on Mifeprex's labeling from "doctor" to "healthcare provider" so that healthcare providers licensed to prescribe drugs under state law could prescribe mifepristone. FDA reviewed data including four studies of 3,200 women prescribed mifepristone by nurses and certified nurse midwives; none showed a statistical difference in outcomes from physician-

prescribed mifepristone. J.A. 461. FDA concluded that this "clearly demonstrates that efficacy is the same with non-physician providers," *id.*, and that "it is safe for [such] providers to administer medical abortion," J.A. 497; *see* J.A. 495-498.

iii. Adverse-event reporting

FDA analyzed the data and literature for information about adverse events in support of its decision to modify a requirement that Mifeprex prescribers report all serious adverse events. Based on its analysis of 15 years of such reporting, FDA concluded that "the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely." J.A. 426. Of the more than 2.5 million women who had taken mifepristone as of 2015, fewer than *one-tenth of one percent* experienced *any* adverse event, and only 0.035% had been hospitalized. J.A. 500-502. The numbers of other serious adverse events are rarer still. *Id.*

Based on this data, FDA found it "appropriate to modify the current adverse-event reporting requirements" for prescribers. J.A. 466. Even after the 2016 changes, anyone can report an adverse event for Mifeprex by calling a 1-800 number on the labeling or submitting a form on FDA's website. *See* FDA, *Mifeprex Prescribing Information* 1 (Jan. 2023);[4] FDA, *MedWatch Online Voluntary Reporting Form*.[5] And like every NDA holder, Danco is required to report to

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[4] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf.

[5] https://www.accessdata.fda.gov/scripts/medwatch/ (last visited Jan. 23, 2024).

FDA all adverse events that it learns of from any source. 21 C.F.R. §§ 314.80, 314.81. Mifeprex prescribers remain obligated to report to Danco—and Danco to FDA—any patient deaths, "whether or not considered drug-related." FDA, *REMS Single Shared System for Mifepristone 200 mg* 5 (Mar. 2023).[6]

2. 2021 Non-Enforcement Decisions And 2023 REMS

During the COVID-19 public health emergency, the American College of Obstetricians and Gynecologists (ACOG) urged FDA to suspend enforcement of the in-person dispensing requirement for mifepristone because it unnecessarily put patients and providers at risk of COVID-19, delayed time-sensitive healthcare, and served "as a barrier to accessing this safe, effective medication." ROA 783. FDA evaluated that issue, including by analyzing medical literature, post-marketing adverse-event reporting from earlier in the pandemic, and information about deviations or noncompliance events associated with the REMS. J.A. 364-365. FDA found no indication that noncompliance or modification of the in-person dispensing requirement had increased adverse events. J.A. 365. FDA's April 2021 response letter to ACOG therefore stated the agency would exercise enforcement discretion as to that requirement. *Id.*

FDA reiterated this analysis and reasoning in its December 2021 response to Respondents' 2019 citizen petition challenging certain of the 2016 changes. Based on the evidence, FDA concluded that

[6] https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2023_03_23_REMS_Full.pdf.

"mifepristone may be safely used without in person dispensing," J.A. 399, and that in-person dispensing was "no longer necessary to ensure that the benefits of the drug outweigh the risks," J.A. 397. FDA relied on safety data from the non-enforcement period, which showed "no indication" that suspending the in-person dispensing requirement "contributed to" adverse events. J.A. 397-398. FDA also pointed to three studies permitting pharmacy dispensing by mail and five studies allowing clinic dispensing by mail, all of which supported the conclusion that mifepristone remains safe and effective without mandatory in-person dispensing. J.A. 402-406.

Based on its analysis, FDA directed Danco to submit an sNDA proposing modifications to the REMS "to remove the in-person dispensing requirement." J.A. 407; *see* J.A. 378-379. Danco complied, and FDA approved Danco's sNDA in January 2023. *See* Ctr. for Drug Evaluation & Rsch., *Approval Package for: Application Number 020687Orig1s025* (Jan. 3, 2023).[7]

C. Procedural History

1. In November 2022, Respondents brought an APA suit challenging FDA's 2000 approval of Mifeprex, FDA's 2016 changes to the labeling, and FDA's 2021 non-enforcement decisions, and asked the District Court to preliminarily enjoin those FDA actions.[8] Danco intervened.

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[7] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/020687Orig1s025.pdf.

[8] Respondents never amended their complaint to challenge the 2023 REMS modifications. The documents on which FDA based the 2021 statements of enforcement discretion and the 2023 REMS modification are not in the record.

All parties agreed to defer Respondents' preliminary-injunction request until after the administrative record was produced. ROA 3240-3252; ROA 3588-3595; ROA 3801-3811. The District Court, however, declined to wait for the record, ROA 4192, and instead entered a ruling purporting to "stay" the long-passed effective dates of each challenged FDA action, Pet. App. 193a-195a (citing 5 U.S.C. § 705). The court found that Respondents had standing, Pet. App. 118a-133a, and that FDA likely acted arbitrarily and capriciously in 2000, 2016, and 2021, *id.* at 159a, 184a-186a. The court also concluded that FDA's 2021 decision to remove the in-person dispensing requirement likely violated the Comstock Act, *id.* at 151a-159a, and that the remaining preliminary-injunction factors favored Respondents, *id.* at 187a-193a.

2. Danco and the Government appealed and sought an emergency stay. The Fifth Circuit left in place the District Court's order as to FDA's 2016 and 2021 actions. *Id.* at 244a.

Danco and the Government submitted emergency stay applications to this Court, which stayed the preliminary injunction in full through the disposition of its review. *Id.* at 245a.

3. The Fifth Circuit merits panel affirmed the District Court's decision to enjoin FDA's 2016 and 2021 actions.

The panel found that Respondents had established associational standing. On injury-in-fact, the panel inferred that, "given the millions of women who take mifepristone, the number of women who experience complications from taking the drug, and the high number of the Organizations' members who treat such

women," "it is highly likely that one or more of their members will be required to provide emergency care to a mifepristone patient in the near future," and in the course of providing care could be injured through wasted resources, liability costs, and conscience violations. *Id.* at 17a, 23a-26a, 31a-32a. On traceability, the panel concluded that these purported injuries are traceable to the 2016 changes and 2021 non-enforcement decisions based on an "increased risk" that more complications and more follow-up care might occur as a result of FDA's actions. *Id.* at 36a-38a. On redressability, the panel offered no reasoning.

On the merits—and although it, too, lacked the administrative record—the panel found that FDA failed to fully consider its decisions, rendering the agency's 2016 and 2021 actions likely arbitrary and capricious.

As to the 2016 changes, the panel concluded that FDA had not sufficiently addressed whether there was a potential "cumulative effect" of the 2016 changes, *id.* at 53a, even though the limited record shows that FDA extensively considered data involving various combinations of the changes, none of which showed any impact on the drug's safety and efficacy profile. The panel also concluded that FDA likely acted arbitrarily and capriciously in continuing mandatory prescriber adverse-event reporting only for fatalities, even though, like with all drugs, prescribers or anyone else can still voluntarily report any adverse event. As the panel saw it, FDA did not sufficiently consider whether "the 2016 Amendments might alter the risk profile." *Id.* at 54a-56a.

As to FDA's 2021 decisions to exercise enforcement discretion on in-person dispensing, the panel concluded that Respondents' challenge was not mooted by the unchallenged 2023 removal of the in-person dispensing requirement. *Id.* at 57a-59a. Based on the panel's view that FDA acted arbitrarily and capriciously in 2016 by narrowing prescribers' mandatory-adverse-event reporting, the panel asserted that FDA could not rely on data in any adverse-event reports as a basis for exercising enforcement discretion. *Id.* at 59a-61a. The panel also faulted FDA for describing medical literature as "not inconsistent with" the agency's conclusion, rather than saying the literature "affirmatively supported" its conclusion. *Id.* at 61a-63a.

The panel also affirmed the District Court's conclusion that Respondents were likely to suffer irreparable harm absent relief, and that the equities favored Respondents. *Id.* at 63a-69a.

The panel rejected remand-without-vacatur because, in its view, and even without knowing what else was in the agency records, FDA would be unable to remedy these purported errors. *Id.* at 72a.

Judge Ho concurred in part and dissented in part. Pet. App. 76a-110a. He agreed with the majority's analysis of FDA's 2016 and 2021 actions but would have also invalidated the 2000 approval and held that FDA's 2021 non-enforcement decisions violated the Comstock Act. *Id.*

SUMMARY OF ARGUMENT

The Firth Circuit erred in affirming the District Court's order preliminarily enjoining FDA's 2016 and 2021 actions.

I. Respondents lack Article III standing to challenge these actions. The court of appeals held that Respondents have standing because some member of a Respondent association may one day treat a woman who is seeking care in the emergency room after she was prescribed mifepristone by a different healthcare provider.

That theory of injury flunks Article III for reasons articulated in multiple decisions of this Court. It rests on claims of having provided past emergency-room care in a few handfuls of isolated situations over the decades in which many millions of women have taken mifepristone, paired with speculation that these isolated instances will recur—none of which adds up to an Article III injury. *Clapper* v. *Amnesty International USA* held that "[a]llegations of *possible* future injury" are insufficient, 568 U.S. 398, 409 (2013) (citation omitted); *City of Los Angeles* v. *Lyons* held that claims of past injury "do not amount to that real and immediate threat of injury necessary to make out a case or controversy," 461 U.S. 95, 103 (1983); and *Summers* v. *Earth Island Institute* held that these rules govern even when claims of past harm are coupled with "a statistical probability that some [plaintiffs] are threatened with concrete injury," 555 U.S. 488, 495, 497 (2009).

Respondents have also failed to show that any claimed injuries are traceable to the 2016 or 2021 actions they challenge, or would be alleviated by the injunction they seek. Respondents are not themselves "the object of the government action or inaction [they] challenge[ ]," and their injuries turn on the independent decisions of multiple third parties—both healthcare providers exercising medical judgment

and women choosing to have a medication abortion—in circumstances that do not involve and are unknown to Respondents. *Lujan* v. *Defs. of Wildlife*, 504 U.S. 555, 562 (1992). Respondents are left offering "speculation about 'the unfettered choices made by independent actors not before the court,'" *Clapper*, 568 U.S. at 414 n.5 (quoting *Lujan*, 504 U.S. at 562), which defeats traceability and redressability.

II. On the merits, the Fifth Circuit erred in enjoining FDA's 2016 and 2021 actions. Before enjoining agency action as arbitrary and capricious for failure to consider some aspect of a problem, a court must know what is included in "the full administrative record that was before the [agency] at the time [it] made [its] decision." *Citizens to Pres. Overton Park, Inc.* v. *Volpe*, 401 U.S. 402, 420 (1971), *abrogated on other grounds*, *Califano* v. *Sanders*, 430 U.S. 99 (1977). Otherwise, the court is simply speculating about what the agency considered. There is no debate that the record here is incomplete.

Even the limited record that was before the lower courts, however, demonstrates that FDA's 2016 and 2021 actions were "reasonable and reasonably explained." *FCC* v. *Prometheus Radio Project*, 592 U.S. 414, 423 (2021). The available record contains no basis to overturn FDA's considered scientific judgment. The Fifth Circuit questioned whether FDA had sufficiently considered the potential "cumulative effect" of the 2016 changes, even though FDA's reasoned scientific judgment was that the available evidence demonstrated zero additional safety or efficacy concerns from the modifications. The court questioned FDA's 2016 decision that some of the mandatory prescriber adverse-event reporting was no

longer necessary, even though the evidence showed it was no longer warranted in the face of Mifeprex's established safety profile. And the court disagreed that FDA had enough evidence to warrant exercising enforcement discretion as to in-person dispensing in 2021, even though FDA comprehensively explained why both real-world data and scientific literature supported that conclusion.

The Fifth Circuit's decision to enjoin drug labeling that had been in place for years was entirely unprecedented. It was destabilizing to the pharmaceutical industry, which relies on courts applying narrow, deferential review to FDA's scientific assessments. It posed serious risk to women and teenage girls, including pushing them to later-stage, more invasive surgical abortions, and to resource-constrained public healthcare systems, including by reimposing requirements of multiple in-person physician visits that do not improve outcomes. It also directly injured Danco, whose only product is Mifeprex, as Danco outlined in its emergency stay application. Stay App., No. 22A901, Long Decl. ¶¶ 3-4, 11-28.

Given all of these serious harms, coupled with the lack of impending injury and federal and state conscience statutes that—when invoked—*protect* Respondents and their members, the unprecedented act of enjoining FDA's determination of a drug's required conditions of use was improper. Even if there was anything to the Fifth Circuit's purported concerns (and there was not), the court should have obtained the entire record and provided FDA an opportunity to address those concerns before acting to effectively remove a long-used drug from the market

for an unknown length of time and requiring a return to outdated labeling for patients and providers.

Reversal is warranted.

ARGUMENT

I. RESPONDENTS LACK STANDING.

Respondents claim to have associational standing to challenge FDA's 2016 and 2021 actions. As relevant here, an association has standing on behalf of its members when "its members would otherwise have standing to sue in their own right." *Hunt* v. *Wash. State Apple Advert. Comm'n*, 432 U.S. 333, 343 (1977). To satisfy that requirement, Respondents must show that at least one of their members "suffered an injury in fact"; the injury is "fairly traceable" to FDA's actions; and it is "'likely,' as opposed to merely 'speculative,' that the injury will be 'redressed by a favorable decision.'" *Lujan*, 504 U.S. at 555, 560-561 (citation and alterations omitted). Respondents cannot show even one of these, much less all three.

A. No Association Member Faces Certainly Impending Injury From FDA's 2016 Or 2021 Actions.

To have standing to seek injunctive relief, a plaintiff must establish facts showing an injury that is "certainly impending," which requires something more than an "objectively reasonable likelihood." *Clapper*, 568 U.S. at 410 (citation omitted). A plaintiff cannot rest on "[a]llegations of *possible* future injury," *id.* at 409 (citation omitted), or "past wrongs," because such assertions do not "amount to that real and immediate threat of injury necessary to make out a case or controversy," *Lyons*, 461 U.S. at 103. Nor can

a plaintiff bolster claims of past harm with "a statistical probability" of injury to some association member; to hold otherwise "would make a mockery of [this Court's] prior cases." *Summers*, 555 U.S. at 495, 497-498. Respondents failed to offer facts demonstrating an association member faces such certainly impending injury.

1. Respondents Rely On Statistics Rather Than Identifying An Association Member Facing Actual, Imminent Injury.

Asserting a statistical possibility of injury is categorically insufficient to establish associational standing. An injury-in-fact must be "actual and imminent, not conjectural or hypothetical." *Summers*, 555 U.S. at 493, 497. For that reason, although an organization *can* sue on behalf of its members "[e]ven in the absence of injury to itself," *Hunt*, 432 U.S. at 342 (citation omitted), an association *cannot* merely rely on the size of its membership to prove that it has standing, *Summers*, 555 U.S. at 497-498.

Instead, this Court has consistently "required plaintiff-organizations to make specific allegations establishing that at least one identified member had suffered or would suffer harm." *Summers*, 555 U.S. at 498. *Summers*, for instance, held that organizations lacked associational standing to challenge a Forest Service regulation even though they had "thousands of members" who "use[d] and enjoy[ed]" areas affected by the regulation and there was "a statistical probability that some of those members [were] threatened with concrete injury." *Id.* at 497-498 (citation omitted). Likewise, *Lujan* held that organizations lacked associational standing to

challenge a rule concerning wildlife funding because they had not shown "that one or more of [their] members would thereby be directly affected apart from their special interest in th[e] subject." 504 U.S. at 563 (citation and quotation marks omitted).

Here, Respondents' affidavits do not support the conclusion that any particular member faces certainly impending injury from FDA's 2016 or 2021 actions. Some declarants speculate about what "may," "could," or "might" occur if they happen to be working in an emergency room when an unknown future patient needs unknown future care. *E.g.*, J.A. 166-167. None assert that they have a regular practice of providing follow-up care to women who chose to have a medication abortion using mifepristone prescribed by another provider. The court of appeals plainly erred in holding that assertions of possible future harm to unidentified members in uncertain circumstances meets Article III's injury-in-fact requirement.

The Fifth Circuit wrongly described its decision as consistent with *Summers*. According to the court, because certain doctors stated they had previously treated a woman who experienced complications from mifepristone, these "prior instances" of care in combination with "mifepristone's continued availability" showed that Respondents' "members are reasonably likely to be injured again." Pet. App. 28a. That reasoning is precisely the sort of probabilistic inquiry *Summers* expressly denounced.

In *Summers*, the majority specifically rejected the suggestion that the "requirement of imminent harm" could be "replace[d]" with "a realistic threat" that proven, past conduct would "recur[] * * * in the reasonably near future." *Summers*, 555 U.S. at 499-

500 (quotation marks and emphasis omitted) (quoting *id.* at 505 (Breyer, J., dissenting)). A statement by a Respondent-association member that she (or a colleague) previously treated a woman for complications related to a medication abortion cannot excuse Respondents' failure to identify a member facing an imminent risk of future harm from FDA's 2016 or 2021 actions. Mifeprex has been approved for medication abortion since 2000. Pointing to a handful of past incidents over 20+ years, as the court of appeals did, is no substitute for concrete, impending future injury from the specific 2016 or 2021 use-condition changes that is personal to an individual association member. *See id.* at 495-496 (no standing where affiant engaged in conduct hundreds or thousands of times in the past).

Respondents are in a worse position than even the *Summers* plaintiffs because their claims of past injury primarily refer to care some *other* doctor provided, point to *undated* experiences that may predate or be unrelated to the use-condition changes made in 2016 or 2021, and lack facts showing that any woman treated in the emergency room had been prescribed FDA-approved mifepristone. For example, although Dr. Skop claims that during her decades of practice, she has "cared for at least a dozen women who have required surgery," the statement is carefully phrased in the passive voice; Dr. Skop never specifies whether *she* performed these surgeries herself, whether *another physician* could have stepped in if she preferred not to, *in what year* this care occurred, and *whether* the patient had been validly prescribed FDA-approved mifepristone by another provider. J.A. 163; *see also, e.g.*, J.A. 154 (declarant's "partner" provided "critical care"); J.A. 163 (declarant's "group practice

admitted three women"); J.A. 153 (patient took unapproved drug "from India").

Moreover, because the legal landscape has recently changed dramatically, past instances are less relevant. At most, Respondents' declarants assert they know about one to two patients *a year* who presented to an emergency room with a "chemical abortion" related complaint. And that was *before* the States in which most declarants practice restricted medication abortion after *Dobbs* v. *Jackson Women's Health Organization*, 597 U.S. 215 (2022). The limitations on, or complete unavailability of, medication abortion under state law where declarants work further shrinks the already tiny fraction of hypothetical women any declarant could potentially encounter in an emergency room.[9]

Ultimately, Respondents' associational standing theory fails to pinpoint any specific member facing concrete, non-speculative, imminent harm by FDA's 2016 or 2021 actions. The Fifth Circuit's decision accepting it makes the same "mockery of [this Court's] prior cases" that *Summers* condemned. 555 U.S. at 498.

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[9] *See, e.g.*, Tex. Health & Safety Code § 171.204 (2021) (banning abortion after detection of fetal heartbeat); *id.* § 171.063 (2021) (where not already prohibited, restricting medication abortion to physician-only prescribing; requiring in-person dispensing; prohibiting mailing); Ind. Code §§ 16-34-2-1 (2021), 16-18-2-327.9 (2022) (banning most abortions); *id.* §§ 25-1-9.5-0.5 (2021), 16-34-2-1.1(a)(5) (2022) (where not already prohibited, prohibiting telehealth abortion care; requiring waiting period and ultrasound); Ga. Code § 16-12-141(b) (2019) (banning abortion after detection of fetal heartbeat); *id.* § 31-9A-3 (2020) (where not already prohibited, restricting medication abortion to physician-only prescribing).

2. Respondents' Speculative Claims Of Future Injury Depend On Attenuated Chains Of Third Parties' Choices.

The Fifth Circuit's bad math does not add up to non-speculative injury to a Respondent-association member. The court's future-injury analysis was based on (a) the fact that "millions of women" have taken mifepristone since its 2000 approval; (b) an (unsupportable) assertion that "a definite percentage of women who take mifepristone will require emergency-room care"; and (c) supposed "testi[mony] that hundreds of [Respondents'] members are OB/Gyns and emergency-room doctors who care for women in these circumstances." Pet. App. 26a. The panel reasoned that this combination made it "highly likely that one or more of [Respondents'] members will be required to provide emergency care to a mifepristone patient in the near future." *Id.* at 17a, 23a-24a. Every step of that analysis was wrong.

First, there are no record facts showing the number of women who were prescribed mifepristone after the 2016 or 2021 actions and would not otherwise have been prescribed the drug. But only that incremental group of women is relevant to whether an association member faces injury from the use-condition changes made in 2016 or 2021. The Fifth Circuit's analysis was wrong from the start because its "millions of women" who have taken mifepristone premise counts *all women who have taken the drug since its 2000 approval*. The actual starting point for any statistical calculation would have to be the number of *additional* women who have taken or will take Mifeprex as a result of the specific

changes in 2016 or 2021. That number is not in the record.

Second, there is no factual basis in the record for the statement that a "definite percentage" of women will seek emergency-room care as a result of FDA's 2016 or 2021 actions. The extensive study data that FDA relied on in 2016 showed that, on average, 97.4% of women (US studies) and 96.1% of women (non-US studies) need *no intervention of any kind*. *See supra* pp. 7-8. Since Mifeprex's 2000 approval, serious adverse events of any kind have been "exceedingly rare," J.A. 465, including a rate of post-use hospitalization well below 1%, *see supra* p. 10. And when some sort of additional intervention is needed, it can (and often does) occur through further follow-up with the original prescriber or at a location the original prescriber has directed the patient to go, which may be any number of locations other than an emergency room where a Respondent-association member is working. J.A. 309-310; *see also* FDA, *Mifeprex Prescriber Agreement Form* 1 (Mar. 2023)[10] (directing that prescribers either have the "[a]bility to provide surgical intervention" or "ma[k]e plans to provide such care through others").[11]

No facts in the record show any women—let alone a "definite percent"—who will certainly seek emergency-room care. But any valid statistical

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[10] https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2023_03_23_Prescriber_Agreement_Form_for_Danco_Laboratories_LLC.pdf.

[11] A second dose of misoprostol results in the avoidance of any surgical follow-up for 90% of the small percentage of women for whom the initial mifepristone-misoprostol regimen does not result in a complete treatment. J.A. 461.

analysis of future injury would require knowing the fraction of women who will need further care as a result of the 2016 or 2021 actions, and the even smaller fraction who will seek such care at an emergency room. That number is not in the record.

Third, there are no facts in the record showing how often a Respondent-member will be working in an emergency room and obligated to provide care to a woman who took mifepristone because of the 2016 or 2021 actions. The record does not even show the total number of individual emergency-room doctors among the associations' memberships, let alone where or how often they work. But when trying to establish a probability of harm to an association member, these facts matter—one association describes itself as for pediatricians; another for dentists; a third welcomes retired, foreign, and non-practicing doctors of many specialties; and the fourth association is comprised of the other three. J.A. 9-11; *see* AAPLOG, *Join AAPLOG Today!* [12] Even knowing how many individual, practicing emergency-room doctors are among these membership rolls would not speak to any statistical likelihood of one of them being obligated to treat a particular woman; that would turn on a whole other array of facts like what percentage of time the member is the only doctor available, which in turn would require knowing, among other things, where and how often those members practice, how many doctors make up the staff in those locations, and what alternative facilities or practitioners could provide emergency care to any given individual when she needs it. Again, none of that is in the record.

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[12] https://aaplog.org/become-a-member/ (last visited Jan. 23, 2024).

The bottom line: Respondents' claims of threatened injury "rel[y] on a highly attenuated chain of possibilities," including "speculation about the decisions of independent actors"—both healthcare providers and women choosing to have a medication abortion. *Clapper*, 568 U.S. at 410-414. This Court already rejected that approach as "necessarily conjectural." *Id.* at 412. Whatever "certainly impending" means, it is more than a percentage of a fraction of a portion of a possibility.

3. Respondents Offer No Facts Showing Their Asserted Injuries Ever Occurred.

The Fifth Circuit described three possible injuries that it said could occur if a woman sought care in an emergency room after taking mifepristone: Respondents' members (1) could be forced to "choose between following their conscience and providing care," causing "mental and emotional stress," Pet. App. 32a, 34a-35a; (2) might have to "divert time and resources away from their regular patients," *id.* at 31a; and (3) might face a risk of "greater liability and increased insurance costs," *id.*

Respondents' declarations fail to substantiate that a member was or could be unable to raise a conscience objection to providing care, or that any member's liability or insurance costs are any different for treating a patient after a medication abortion than for any other patients. And the mix of patients an emergency-room doctor treats on a given shift is not a cognizable Article III injury, nor was a diversion-of-care injury factually demonstrated here. Emergency-room doctors, after all, lack "regular patients"; their job is to provide care to whomever needs it.

The declarants also obliquely reference past objections of *other* healthcare providers (who they do not allege are Respondent-association members) or care that the declarants apparently provided without objection.[13] For example, Dr. Francis describes an incident in which her "*partner* felt * * * forced to participate in something that she did not want to be a part of," but never states this partner is a Respondent-association member or raised a conscience objection. Pet. App. 32a (quoting J.A. 154) (emphasis added); *see also id.* (citing dental-association member and non-physician declarations expressing future "concerns" about unspecified *other* members, again without addressing statutory conscience rights, J.A. 142-143; J.A. 120-121). And although Dr. Skop states that she has "cared for at least a dozen women who have required surgery," she does not allege that she herself had to perform the surgery or provide other care, let alone that she raised a conscience objection that was denied. *Id.* (quoting J.A. 163). Similarly, Dr. Wozniak states that she once treated a woman who had previously been "advised" that medication abortion was "contraindicated" for her, without ever asserting the treatment violated Dr. Wozniak's conscience or that she raised a conscience objection. J.A. 173.

There are similar gaps in the allegations concerning economic and resource injuries. No declarants describe accusations of malpractice or

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[13] *See* 42 U.S.C. §§ 238n, 300a-7(c), (d) (federal conscience protections); Consolidated Appropriations Act, Pub. L. No. 117-103, Div. H, Tit. V, §§ 506-507 (2022) (similar); Nadia N. Sawicki, *Protections from Civil Liability in State Abortion Conscience Laws*, 322 J. Am. Med. Ass'n 1918, 1918 (2019) ("State conscience laws typically provide additional protections that supplement those established by federal antidiscrimination law.").

increased insurance costs in the 20 years mifepristone has been available, nor have they (or can they) tie any such claims to the 2016 or 2021 actions. *See* J.A. 292; *e.g.*, J.A. 142. Nor do the declarants describe any "regular patients" or offer facts showing that an emergency room lacked resources to care for other patients as a result of women prescribed mifepristone under FDA's 2016 or 2021 actions—even assuming it would be Article III cognizable injury for an emergency-room doctor to have to triage among individuals seeking care. The only reference to a so-called resource diversion does not link that diversion to any injury. *See* Pet. App. 25a (explaining that because Dr. Francis "spent several hours" with one patient she had to "call in an additional physician to help cover" other patients in the labor and delivery unit).

Because each element of standing must "be supported in the same way as any other matter on which the plaintiff bears the burden of proof," *Lujan*, 504 U.S. at 561, at the preliminary-injunction stage, a movant must make a "clear showing" of its entitlement to such relief, *Winter* v. *Nat. Res. Def. Council, Inc.*, 555 U.S. 7, 22 (2008); *see also Summers*, 555 U.S. at 499 (parties must make "a factual showing of perceptible harm" (citation omitted)). Respondents failed to do so.

B. Respondents' Alleged Injuries Are Not Traceable To FDA's 2016 Or 2021 Actions Or Redressable By This Court.

Standing also requires that Respondents' asserted injuries be attributable to the specific agency action challenged and alleviated by the judicial ruling they

seek. *Lujan*, 504 U.S. at 560. Respondents fail in both respects.

1. An injury suffices for Article III standing only if it is "fairly traceable to the challenged action of the defendant, and not the result of the independent action of some third party not before the court." *Id*. (citation, brackets, and ellipses omitted). Although that principle "does not exclude" any non-regulated party from ever demonstrating traceability, *Bennett* v. *Spear*, 520 U.S. 154, 169 (1997), it does mean that standing is "substantially more difficult to establish" when a party is not regulated by the challenged action, *Lujan*, 504 U.S. at 562 (citation and quotation marks omitted). That is because a plaintiff cannot establish standing simply by showing that the defendant's conduct creates the *possibility* of injury. *Clapper*, 568 U.S. at 417.

Yet mere possibility is all that ties Respondents to FDA's 2016 and 2021 actions. Respondents' theory of standing depends on the independent decisions of healthcare providers and their patients—neither of whom are coerced by FDA to behave in a particular way. *Id.* at 412. Because Respondents cannot predict the medical judgment of third-party healthcare providers who choose to prescribe mifepristone, or the discretionary actions of third-party patients who choose to have a medication abortion, Respondents' evidence "does not adequately trace the necessary connection" between FDA's 2016 and 2021 actions and any purported injury. *California* v. *Texas*, 141 S. Ct. 2104, 2118-19 (2021).

The Court has consistently looked for that predictability to bridge the gap created by third-party decisionmaking. In *Bennett*, for example, the Court

found that the plaintiffs had standing to challenge a Fish and Wildlife Service opinion even though the Bureau of Reclamation retained ultimate responsibility for determining whether the project would go forward. 520 U.S. at 158-160, 168-169. The Court found standing because the Bureau would risk civil and criminal penalties if it disregarded the Service's opinion, making the opinion "virtually determinative." *Id.* at 169-170. By contrast, in *Clapper*, the Court held the plaintiffs lacked standing to challenge a federal surveillance statute that "at most authorizes—but does not mandate or direct—the surveillance that [plaintiffs] fear." 568 U.S. at 411-412. *Clapper*'s holding maps directly onto this case: The challenged 2016 and 2021 actions permit but do not require a particular action by healthcare providers who prescribe mifepristone and by patients who choose to take it, defeating traceability. *Id.* at 412.

That makes this case unlike *Department of Commerce* v. *New York*, where this Court found States had standing to challenge a citizenship-based census question even though the States' financial injuries depended on people not responding if the census included the question. 139 S. Ct. 2551, 2565-66 (2019). The multi-thousand-page administrative record showed that the challenged question historically resulted in significant undercounting and would continue to do so at a predictable rate. *Id.* at 2564-65. Respondents here do not use historical data to predict a specific rate of emergency-room visits for a declarant's hospital based on FDA's 2016 and 2021 actions. They offer no facts demonstrating that the rate of emergency-room visits to that hospital will necessarily affect any declarant, or require that

declarant to provide any specific care. They likewise cannot accurately predict how third-party doctors or those doctors' patients would act in the future.

2. Respondents also must "demonstrate standing for each claim that they press and for each form of relief that they seek." *TransUnion LLC* v. *Ramirez*, 594 U.S. 413, 431 (2021). Respondents have never attempted to separate injuries allegedly traceable to FDA's 2016 or 2021 actions from those that would have occurred anyway based on mifepristone's original approval. That leaves Respondents unable to demonstrate traceability. "[H]arm from one particular inadequacy in government administration" does not create standing to challenge "all inadequacies in that administration." *Lewis* v. *Casey*, 518 U.S. 343, 357 (1996); *see, e.g.*, *California*, 141 S. Ct. at 2119-20 (no standing to challenge minimum-essential-coverage provision of the Affordable Care Act where injuries were caused by other statutory provisions).

Respondents have not and cannot identify the doctors, patients, hospitals, times, or circumstances that would lead a member to treat a patient for harm resulting from FDA's 2016 or 2021 decisions, which would not have occurred under the 2000 approval. The Fifth Circuit's simple solution was to say that FDA's 2016 and 2021 actions "will increase the number of women who suffer complications as a result of taking mifepristone." Pet. App. 36a. But even if that (factually wrong) assertion somehow amounted to a certainly impending injury for a Respondent-association member, it does not solve this separate standing problem: Traceability speaks to the "causal connection between the injury and the conduct

complained of," not the risk that the injury will occur. *Lujan*, 504 U.S. at 560.

3. Respondents also bear the burden of showing that they will "benefit in a tangible way from the court's intervention." *Steel Co.* v. *Citizens for a Better Env't*, 523 U.S. 83, 103 n.5 (1998) (citation omitted). The Fifth Circuit did not address redressability, despite acknowledging the "rigorous evidence" necessary to prove it. Pet. App. 36a. Respondents' redressability arguments fail for all the same reasons that their injury and traceability arguments fail. *Cf., e.g.*, *Simon* v. *E. Ky. Welfare Rts. Org.*, 426 U.S. 26, 28, 42-43 & n.23 (1976) (plaintiffs lacked standing where it was "purely speculative" whether a decision "allowing favorable tax treatment" to hospitals that limited services for indigents would result in hospitals providing less indigent care). But there are other reasons, too. Principal among them: Because FDA's actions made Mifeprex more effective and further reduced adverse events, Respondents' requested relief—returning to the pre-2016 labeling—would make it *more*, *not less*, likely that women who are prescribed mifepristone will need additional intervention. *Compare* J.A. 450 (92% need no intervention under original labeling) *with supra* pp. 7-8 (96.1% and 97.4% of women need no intervention under 2016 changes).

C. Ruling For Respondents Would Require Fundamentally Rewriting Standing Doctrine.

The decisions that the court of appeals pushed past to find standing for these Respondents to assert these claims—*Clapper*, *Summers*, *Lujan,* and *TransUnion*—all police the boundaries of standing for

issue-oriented advocacy groups. The Court has repeatedly emphasized that relaxing Article III standing requirements would amount to an expansion of judicial power vis-a-vis the other branches of government. *E.g.*, *TransUnion*, 594 U.S. at 422-423; *United States* v. *Texas*, 599 U.S. 670, 675-676 (2023). This Court should not create special standing rules for medical associations.

All drugs have side effects and complication risks, so the Fifth Circuit's reasoning would bless any suit by an association of healthcare providers challenging any agency decision that might affect a potential patient. Some anti-depressants can increase risks of suicidal thoughts; some drugs to treat one form of cancer can increase the risk of another; some drugs cause birth defects; the list goes on. And FDA is not the only agency whose actions affect health and safety. Some doctors dislike recommended vaccines; others dislike lifting mask mandates. Pediatricians might dislike easing air pollution regulations, which might cause more children to need treatment for severe asthma, taking time away from other patients. Emergency-room doctors might dislike easing gun restrictions, or laws eliminating workplace protections like mandatory water breaks on hot days, or the way a car seat recall is being handled—all of which could result in a patient seeking care in an emergency room someday.

There is no way to limit such sweeping changes to standing doctrine to medical professionals. Teacher associations could challenge regulations they believe affect students in a way that disrupts the classroom; associations of firefighters could challenge regulations of products they say present fire risks. And so on.

This Court's standing precedents—unlike the decision below—ensure that an unregulated party's disagreement with governmental policy is not a sufficient basis to challenge that policy.

Respondents are outside the limited types of plaintiffs with Article III standing to challenge regulatory decisions concerning someone else's product. They are not consumers of Danco's product.[14] They do not sell or advertise it.[15] They do not manufacture a competing product.[16] And they are not the "object of the action * * * at issue": Respondents' members do not prescribe mifepristone for abortion, or seek to treat patients who have taken mifepristone in an elective abortion. *Lujan*, 504 U.S. at 561. Nor are they required to do so by any FDA action challenged in this case. *Mercury-Free Drugs*, 671 F.3d at 1280-81. In short, Respondents are unaffected in an Article III sense by FDA's labeling of mifepristone.

II. RESPONDENTS' MERITS ARGUMENTS FAIL.

Arbitrary-and-capricious review is "narrow," *Motor Vehicle Mfrs. Ass'n* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983), and "deferential,"

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[14] *Cf., e.g.*, *Merck Sharp & Dohme Corp.* v. *Albrecht*, 139 S. Ct. 1668, 1675 (2019); *see also Coal. for Mercury-Free Drugs* v. *Sebelius*, 671 F.3d 1275, 1281 (D.C. Cir. 2012) (collecting cases "permitt[ing] consumers of a product to challenge agency action that prevented the consumers from purchasing a desired product").

[15] *Cf., e.g.*, *FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 129 (2000).

[16] *Cf., e.g.*, *Monsanto Co.* v. *Geertson Seed Farms*, 561 U.S. 139, 154-155 (2010); *Bristol-Myers Squibb Co.* v. *Shalala*, 91 F.3d 1493, 1497-99 (D.C. Cir. 1996).

Prometheus, 592 U.S. at 427. "[A] court may not substitute its own policy judgment for that of the agency." *Prometheus*, 592 U.S. at 423. After "review [of] the whole record," 5 U.S.C. § 706, the court's role is "simply" to determine whether the agency "acted within a zone of reasonableness," *Prometheus*, 592 U.S. at 423.

The Fifth Circuit erred in holding FDA's 2016 and 2021 actions likely arbitrary and capricious based on the agency's supposed failure to consider all aspects of the problem before it, when the *court itself* did not have all aspects of the problem before it. The court faulted FDA without reviewing the whole record, but even the limited preliminary-injunction record shows that FDA appropriately exercised its predictive judgment based on the evidence before it and reasonably explained its decisions.

A. Respondents Cannot Obtain Relief Without The Administrative Record.

Judicial review of agency action must be "based on the *full* administrative record that was before the [agency] at the time [it] made [its] decision." *Overton Park*, 401 U.S. at 420 (emphasis added). That rule is dictated by the APA and common sense: The statute provides that "the court shall review the whole record" in assessing the legality of agency action, 5 U.S.C. § 706, and under arbitrary-and-capricious review, the agency's "decision ha[s] to be judged by the information then available to it," and "the validity of that action must 'stand or fall * * * on the administrative record made,'" *Vt. Yankee Nuclear Power Corp.* v. *NRDC*, 435 U.S. 519, 549, 553 (1978).

The documents before the Fifth Circuit constituted a fraction of the administrative record. For the 2016

changes, the documents available to the court were FDA's final letter approving the changes; Respondents' citizen petition and FDA's denial; and a few of FDA's internal documents. J.A. 284-291; J.A. 322-347; J.A. 373-412; J.A. 293-320; J.A. 418-525; ROA 2251-2337. For the 2021 decision, the court considered only the correspondence with ACOG and the December 2021 citizen petition denial—no internal FDA documents. ROA 783-785; J.A. 364-365; J.A. 371; J.A. 373-412.

That is why *all* the parties had agreed the District Court should defer ruling on Respondents' preliminary-injunction request until FDA produced the record. *See* ROA 3240-3252; ROA 3588-3595; ROA 3801-3811. Although one panel member expressed concern about ruling on Respondents' claims without the full record, *see* 5th Cir. Oral Arg. 22:23-24:43 (May 17, 2023), the Fifth Circuit ultimately faulted FDA for failing to consider important aspects of the problem *without even knowing the full scope of the agency's consideration*.

The Fifth Circuit described its review as "searching and careful," Pet. App. 52a (quotation marks omitted), but a searching and careful review of a few chapters of a book doesn't mean you've reviewed the book. The court never considered whether there might be other review documents, including statistical reviews, clinical reviews, risk assessment and mitigation analysis, REMS assessments, or correspondence with Danco, that might bear on the reasonableness of the agency's decisions.

The procedural posture of this case does not cure the Fifth Circuit's rush to judgment. To be sure, a partial record may sometimes suffice to resolve an

APA challenge—like in cases asking whether the agency failed to act within statutory or regulatory constraints, *see, e.g.*, *Am. Bankers Ass'n* v. *Nat'l Credit Union Admin.*, 271 F.3d 262, 266 (D.C. Cir. 2001), or cases presenting justiciability problems, *In re United States*, 583 U.S. 29, 32 (2017) (per curiam)—but a request for a preliminary injunction does not permit a court to set the APA aside. "[T]he burdens at the preliminary injunction stage track the burdens at trial," *Gonzales* v. *O Centro Espirita Beneficente Uniao do Vegetal*, 546 U.S. 418, 429 (2006), and Respondents' complaints about the reasonableness of FDA's decisionmaking process and thoroughness of its explanation are precisely the sort of claims requiring review of "the full administrative record," *Overton Park*, 401 U.S. at 420. Thus, just like at the merits stage, proceeding without the complete record on a preliminary injunction means the court is "merely speculating" as to the "basis" for "the agency action the plaintiff seeks to enjoin." *Am. Bioscience, Inc.* v. *Thompson*, 243 F.3d 579, 580-582 (D.C. Cir. 2001).

B. The Existing Record Shows FDA's 2016 And 2021 Actions Were Reasonable And Reasonably Explained, As Required By The APA.

Even on the limited preliminary-injunction record, however, FDA's 2016 and 2021 actions satisfy the narrow arbitrary-and-capricious standard. FDA comprehensively detailed the evidence supporting each decision, made reasonable predictive judgments based on the data, and explained why the evidence supported labeling changes. In holding Respondents were likely to succeed in showing otherwise, the Fifth Circuit did exactly what this Court's precedents

prohibit: It "second-guess[ed]" FDA's "scientific judgment," *Cytori Therapeutics, Inc.* v. *FDA*, 715 F.3d 922, 927 (D.C. Cir. 2013) (Kavanaugh, J.), and "substitute[d] its own policy judgment for that of the agency," *Prometheus*, 592 U.S. at 423. Its decision should be overturned.

Even if there was anything to the Fifth Circuit's purported concerns (and there was not), the court should have remanded without vacatur to allow FDA an opportunity to address these purported shortcomings in the first instance—particularly given the disruptive effects of effectively removing a long-used drug from the market for an unknown length of time and requiring a return to outdated labeling for patients and providers. *See, e.g.*, *Apache Corp.* v. *FERC*, 627 F.3d 1220, 1221 (D.C. Cir. 2010) (Kavanaugh, J.) (remand without vacatur appropriate where "there is 'a serious possibility that the [agency] will be able to substantiate its decision on remand'" (quoting *Allied-Signal, Inc.* v. *U.S. Nuclear Regul. Comm'n*, 988 F.2d 146, 151 (D.C. Cir. 1993))); *A.L. Pharma, Inc.* v. *Shalala*, 62 F.3d 1484, 1492 (D.C. Cir. 1995) (remanding without vacatur to determine whether FDA approval was justifiable because vacatur would "prove disruptive" to sponsor, "which ha[d] relied on" drug approval "in good faith for over thirteen years"); *see also infra* pp. 52-54.

1. FDA Carefully Analyzed And Reasonably Explained Its Approval Of Changes To Mifeprex's Labeling.

In 2016, FDA approved several changes to Mifeprex's labeling. FDA approved changing the dosing regimen and updating the gestational age cutoff. *Supra* pp. 6-8; *see* 21 U.S.C. § 355(d)(5). FDA

also approved modifications to the REMS: reducing the number of in-person clinical visits and allowing other healthcare providers qualified under state law to prescribe Mifeprex. *Supra* pp. 8-10; *see* 21 U.S.C. § 355-1(g)(4)(A).

Based on the evidence before it, FDA's decision to approve these changes was "reasonable and reasonably explained." *Prometheus*, 592 U.S. at 423.[17] FDA's determination was rooted in an exhaustive review of more than 20 years of clinical and real-world data. J.A. 435. Across hundreds of pages, a team of experts carefully analyzed over 90 sources, J.A. 509-516, including over 50 unique studies covering tens of thousands of women, many of which specifically addressed each change FDA was considering:

- twenty-two studies including over 35,000 women supporting the conclusion that the new dosing regimen remained safe and effective, J.A. 446-450; J.A. 478-479;
- seven studies including 934 women supporting the conclusion that the new drug regimen was safe and effective up to 70 days gestation, J.A. 455-456; J.A. 478-479;
- seven studies including 4,018 women supporting finding a repeat dose of misoprostol was safe and effective, J.A. 460-461; J.A. 481-482;
- eleven studies including 30,763 women supporting finding home administration of

[17] Respondents abandoned any challenge to individual changes; they argued below only that the 2016 changes violated the APA because FDA could not point to a study evaluating those changes "as a whole." Appellees Br. 52-55 (5th Cir. May 8, 2023).

misoprostol was comparably effective and safe as compared to in-office administration, J.A. 458-459; J.A. 479-481;

- four studies including 3,200 women supporting the conclusion that allowing non-physician prescribing of Mifeprex would be safe and comparably effective to results from physician prescribers, J.A. 461-462; J.A. 497-498; and
- one study involving over 45,000 women supporting increased flexibility for follow-ups, showing this was "safe to approve," J.A. 485; J.A. 462; J.A. 482-485.

After carefully reviewing these studies, alongside 15 years of real-world data showing Mifeprex's safe use under various conditions, J.A. 478-479; J.A. 506, FDA determined that adopting all the proposed changes would not alter Mifeprex's safety and efficacy profile, J.A. 424-425; 21 U.S.C. §§ 355(d), 356a(b), 355-1(g)(4). As FDA explained, "[t]he submitted efficacy and safety information supported approval of the proposed dosing regimen through 70 days gestation, and other changes." J.A. 317; *accord* ROA 2280-2281. FDA further concluded that "the benefit-risk profile for Mifeprex continues to be favorable and with the agreed-to labeling changes and REMS modifications, the Mifeprex REMS program will continue to assure safe use." J.A. 319; *accord* ROA 2280-2281. In short, FDA evaluated the evidence, explained its conclusions, and reasonably determined that Mifeprex would remain safe and effective under the approved labeling.

The Fifth Circuit reached a contrary conclusion for one reason: According to the court, FDA was required to "consider the cumulative effect" of the 2016 changes

and did not do so. Pet. App. 53a. That argument fails several times over.

First, even the limited record shows that FDA addressed whether Mifeprex would remain safe and effective if the agency approved the interrelated set of changes. 21 U.S.C. §§ 355(d), 356a(b), 355-1(g). FDA relied on many studies of proposed changes in combination. FDA said as much: "As these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes." J.A. 298; *see* J.A. 442. For example, "[f]our studies" including almost 3,000 women "and one systemic review evaluated the exact proposed dosing regimen through 70 days gestation." ROA 2260; ROA 2278. Four studies concerned the at-home administration of misoprostol through 70 days gestation, under both the current and proposed new misoprostol dosing regimen. J.A. 458; *see* ROA 2264-2266. And FDA reviewed three studies evaluating "the safety and efficacy of medical abortion when performed by non-physician healthcare providers" under "the proposed dosing regimen," in which "[a]lmost 1,500 women (over 700 of whom had non-physician care) had gestations through 70 days or more." ROA 2268.

After analyzing this evidence, multiple separate FDA reviewers unanimously recommended approving all the proposed changes. Each reviewer identified all the changes to Mifeprex's labeling that Danco sought; detailed the many studies that addressed various combinations of the changes; explained why those studies supported a safety and efficacy finding; and "recommend[ed] an approval action." J.A. 423; ROA 2254; J.A. 317-319. That is all the APA requires.

In approving labeling changes, FDA is tasked with "evaluat[ing]," based on the information "before" it, whether the drug is safe and effective "under the conditions of use prescribed, recommended, or suggested in the labeling." 21 U.S.C. § 355(d); *see id.* § 355-1(g)(4)(A). FDA satisfied that obligation when it concluded that each of Danco's requested "interrelated" changes posed zero additional safety concerns. J.A. 298. Reviewing courts "may not set aside an agency [action] that is * * * based on consideration of the relevant factors and within the scope of the authority delegated to the agency by the statute." *State Farm*, 463 U.S. at 42. And FDA was "not required to author an essay for the disposition of [Danco's] application"; rather, "[i]t suffices" that "the why and wherefore" can be discerned. *Friedman* v. *FAA*, 890 F.3d 1092, 1099 (D.C. Cir. 2018) (citation omitted).

Respondents and the Fifth Circuit pointed to *no evidence* before FDA that suggested approving the interrelated changes altered Mifeprex's safety profile. They likewise offered *no reason* to believe that adding zero plus zero plus zero additional safety concerns would equal anything other than zero "cumulative" safety concerns, and thus *no basis* to question FDA's predictive judgment that Mifeprex was safe and effective under the revised labeling. *See Prometheus*, 592 U.S. at 425-427 (finding agency's predictive judgment reasonable based "on the data it had (and the absence of any countervailing evidence)"). Agencies are not required to have "perfect empirical or statistical data" before acting. *Id.* at 427. And nothing in the FDCA requires FDA to "conduct its own empirical or statistical studies before exercising its discretion." *Id.*; *see* 21 U.S.C. §§ 355(d), 355-1(g)(4).

The contrary: If FDA concludes based on the "information submitted" in an sNDA that the drug is safe and effective under its proposed labeling, FDA "*shall* issue an order approving the application." 21 U.S.C. § 355(d) (emphasis added).

Second, the court of appeals faulted FDA for not including a lengthier discussion of "cumulative changes," Pet. App. 53a-54a, but Respondents' citizen petition never made any such argument. Plaintiffs cannot "fail[] * * * to bring the matter to the agency's attention," and then "seek[] to have that agency determination vacated on the ground that the agency failed to consider [those] matters." *Vt. Yankee*, 435 U.S. at 553-554 (citation omitted). FDA's detailed response addressed each argument Respondents *did* make and each study they cited. J.A. 379-393.

Third, the Fifth Circuit effectively faulted FDA for not meeting the so-called "study-match" requirement that Respondents argued exists in the FDCA. Under this theory, having multiple clinical trials that study a drug's safety and efficacy under varying protocols is insufficient to allow for scientific decisionmaking about proposed labeling; there must be one clinical trial conducted under the exact "labeled conditions of use" before FDA can find the drug safe and effective. Br. in Opp'n 43. The notion that FDA is required to point to a *single* study "examin[ing] the effect of implementing" every labeling change "together" defies the statutory text. *See* Pet. App. 53a. The FDCA requires only that FDA determine whether "adequate tests" show a drug is safe under its proposed labeling and that the benefits of the drug outweigh its risks. 21 U.S.C. § 355(d); *see id.* § 355-1(g)(4). And virtually

no drug would be approved today if such a study-match requirement existed. Pharm. Cos. Cert. Br. 20.

2. FDA Lawfully Changed The Adverse-Event Reporting Requirements In 2016.

FDA also reasonably explained its conclusion that the pre-2016 mandatory serious-adverse-event reporting for Mifeprex prescribers was no longer necessary in light of the drug's established safety profile and Danco's continuing reporting obligations. J.A. 506; 21 U.S.C. § 355-1(a), (f), (g)(4).

From 2000 to 2016, Mifeprex was subject to the most demanding form of mandatory-adverse-event reporting—something no current REMS requires. Under that regime, Mifeprex prescribers had to report all serious adverse events. J.A. 230. By 2016, FDA had amassed 15 years of data demonstrating Mifeprex's track record as a safe product. J.A. 392; J.A. 500. Of the more than 2.5 million women in the United States who had taken mifepristone by then, more than 99.9% did not experience a serious adverse event. J.A. 501-502. For instance, only 878 women out of the more than 2.5 million who had taken mifepristone—0.035%—were hospitalized. *Id.*

Based on this "well-characterized safety profile," developed over 15 years and millions of patients, FDA decided that mifepristone should be subject to the same adverse-event reporting requirements applied to other drugs, with one heightened requirement remaining. J.A. 392. Under the 2016 decision, prescribers must still report any fatality for any reason, even if unrelated to mifepristone. *Supra* pp. 10-11. Adverse-event reporting for mifepristone thus remains more stringent than for the vast majority of drugs with a REMS; only seven of the 67

REMS mandate adverse-event reporting of deaths. *See* FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS)*.[18] As with other drugs, prescribers, patients, and others can (and do) voluntarily report non-fatal adverse events, such as hospitalizations and blood transfusions, either to Danco directly, or to FDA. *Supra* pp. 10-11. And like all NDA-holders, Danco must share with FDA any adverse events that Danco learns about. *See* J.A. 506; J.A. 392; 21 C.F.R. §§ 314.80, 314.81. Moreover, adverse-event reports are not FDA's only monitoring tool; the agency can also examine scientific literature documenting the drug's safety, *e.g.*, J.A. 299-300, and REMS "assessments," which the drug's sponsor must provide to FDA at regular intervals, 21 U.S.C. § 355-1(d), (g)(2)(B)-(C).

The Fifth Circuit erred in holding that FDA acted arbitrarily and capriciously by modifying the adverse-event reporting requirements for Mifeprex prescribers in 2016. According to the Fifth Circuit, the agency should have kept prescribers' heightened mandatory serious-adverse-event reporting in place *just in case* the 2016 changes altered the drug's safety profile, Pet. App. 55a-56a, even though FDA had just decided based on extensive evidence that they would not.

The court's decision is contrary to the statute, which mandates that these types of REMS requirements be "*necessary* to assure safe use of the drug." 21 U.S.C. § 355-1(f)(1) (emphasis added). The court's decision also re-weighs the scientific evidence, which is improper under arbitrary-and-capricious review. *Marsh* v. *Or. Nat. Res. Council*, 490 U.S. 360,

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[18] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (last visited Jan. 23, 2024).

377 (1989) ("When examining this kind of scientific determination a reviewing court must generally be at its most deferential" (citation and ellipses omitted)). In 2016, FDA determined, based on the available evidence, that serious adverse events under the 2000 approval were exceedingly rare and that the modified labeling would not change the safety profile. *Supra* pp. 6-11. FDA specifically "evaluated the adverse event information" associated with each proposed change. J.A. 308-309. For example, FDA concluded that "data for the proposed regimen," including the revised gestational-age cutoff, "do not suggest a safety profile that deviates from that of the originally approved regimen." J.A. 310; *see* J.A. 304. FDA also found that at-home administration of misoprostol "is associated with exceedingly low rates of serious adverse events, and [comparable] rates of common adverse events" to the 2000 approval. J.A. 308; *see also* J.A. 310 (finding "the evidence demonstrated acceptable safety for each * * * proposed change[]").

FDA thus concluded that (1) Mifeprex's safety profile was established and "essentially unchanged" across 15 years of data; (2) Mifeprex's safety profile would not change as a result of the 2016 changes; and (3) continued mandatory reporting by prescribers of non-fatal serious adverse events was therefore unnecessary. In other words, FDA predicted there would be a comparable number of serious adverse events reported under both the 2000 and 2016 labeling, and given the exceedingly rare number of serious adverse events reported under the 2000 labeling, continued mandatory prescriber-reporting of non-fatal serious adverse events was unnecessary. FDA was well within its right to make this sort of "predictive judgment" "based on the evidence it had."

Prometheus, 592 U.S. at 427. And FDA's path is reasonably discernable. *E.g.*, *Bowman Transp., Inc.* v. *Ark.–Best Freight Sys., Inc.*, 419 U.S. 281, 286 (1974); *Transp. Div. of Int'l Ass'n of Sheet Metal, Air, Rail* v. *Fed. R.R. Admin.*, 40 F.4th 646, 657 (D.C. Cir. 2022) (agency reasonably predicted that "fewer occasions" for situations that can result in injury "would lead to fewer injuries"). The Fifth Circuit erred in holding otherwise.

3. FDA's Actions In 2021 Were Not Arbitrary And Capricious.

The Fifth Circuit should not have even reached Respondents' challenge to FDA's December 2021 non-enforcement decision because that decision is moot. In 2023, FDA superseded its non-enforcement decisions by modifying the REMS to remove the in-person dispensing requirement. *Supra* pp. 11-12. Respondents did not amend their complaint or otherwise raise a challenge to the 2023 REMS. And before the Fifth Circuit, Respondents did not dispute Danco's and FDA's contention that this claim was moot, thereby forfeiting any such argument. Regardless of whether "FDA's policy remains unchanged," Pet. App. 59a, FDA's reasoning for temporarily exercising enforcement discretion no longer matters, because in-person dispensing is no longer a REMS requirement. There is thus no "live dispute" about whether FDA's December 2021 reasoning was deficient. *Contra id.* at 57a.

In any event, FDA's December 2021 decision to suspend the in-person dispensing requirement was reasonable. FDA comprehensively reviewed the data and cogently explained why in-person dispensing was unnecessary. J.A. 378; J.A. 394; J.A. 407; 21 U.S.C.

§ 355-1(f)(1), (g)(4)(B). Even the limited record proves that decision "was the result of a thorough scientific review by experts within [FDA] who evaluated relevant information, including available clinical outcomes data and adverse event reports." J.A. 377.

FDA's decision relied on post-marketing data from adverse-event reports. FDA compared post-marketing data from nearly nine months when in-person dispensing was enforced against data from eleven months when in-person dispensing was not enforced.[19] J.A. 398. "Based on FDA's review of this data, [the agency] concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced." J.A. 399. All of this confirmed to FDA's satisfaction "that mifepristone may be safely used without in-person dispensing," J.A. 399, and that in-person dispensing thus was not necessary to ensure safe use, J.A. 378; *see* 21 U.S.C. § 355-1(f)(1), (g)(4)(B).

FDA also looked to study data. As part of its "extensive review of the published literature," J.A. 399, FDA examined three studies permitting pharmacy dispensing through the mail, one of which showed a mere 0.9% of women experienced an adverse event after taking mifepristone, J.A. 402. These studies also supported finding "that efficacy of medical abortion is maintained with mail order pharmacy dispensing." J.A. 403. FDA also examined

[19] In-person dispensing was suspended twice before: once in response to a court order, from July 2020 to January 2021, and again by FDA in response to the COVID-19 pandemic, in April 2021. J.A. 398. FDA's December 2021 response to Respondents' citizen petition explained that FDA would continue to exercise enforcement discretion with respect to this requirement. J.A. 378.

five studies allowing clinic dispensing by mail, explaining that "these studies overall support that dispensing by mail from clinic is safe and effective." J.A. 403-406.

The Fifth Circuit erred in second-guessing FDA's scientific judgment. The Fifth Circuit offered two purported reasons for its decision. Neither holds up.

First, the Fifth Circuit faulted FDA for relying on adverse-event data. The data showed that a vanishingly small number of women who take mifepristone experience an adverse event, but the court found supposed "limitations" in that data. Pet. App. 59a. The Fifth Circuit criticized FDA for supposedly "eliminat[ing]" the adverse-event reporting requirement in 2016 and then relying on the absence of adverse-event reports in 2021. *Id.* But, as explained, FDA did not eliminate adverse-event reporting; prescribers still must report fatalities, and anyone can still report any other adverse events to FDA or to Danco. *Supra* pp. 10-11. FDA was thus entitled to rely on the adverse-event data relating to mifepristone in 2021, just as FDA relies on that data for other drugs. *Marsh*, 490 U.S. at 377 (deference especially warranted to agency action involving "a high level of technical expertise").

The Fifth Circuit also found FDA's data "insufficient to draw general conclusions about adverse events" because some "adverse events will go unreported" due to the voluntary nature of this system. Pet. App. 59a-60a. But that is true for *every* FDA-approved drug. Indeed, for the vast majority of drugs, prescribers are not even required to report fatalities. *Supra* pp. 45-46. Yet FDA routinely relies on adverse-event data to relax or discontinue a REMS

as prescribers become more familiar with a drug's safety profile. *See* FDA Scholars Cert. Br. 21-22 & n.18; *see also, e.g.*, FDA, *Lotronex sNDA Approval* 2 (Sept. 8, 2023)[20] (eliminating REMS where "[a]dverse event reporting * * * has been stable, and an increase in severe outcomes has not been observed"). It "is not unusual in day-to-day agency decisionmaking" for agencies to rely on imperfect data. *Prometheus*, 592 U.S. at 427. Indeed, if FDA were permitted to modify a REMS only when it has reporting about *all* adverse events, FDA would never be able to modify a REMS. *See* FDA Scholars Cert. Br. 13.

Second, the Fifth Circuit faulted FDA for stating that scientific literature was "not inconsistent with" FDA's conclusion, which it interpreted to mean "the studies neither confirmed nor rejected" the proposed change. Pet. App. 62a (quoting J.A. 400). Wrong again.

FDA made the exact statement the Fifth Circuit was looking for: FDA explicitly said its conclusion was "supported by our review of the published literature." J.A. 397. The Fifth Circuit's conclusion also rests on a flawed premise. An agency decision that relies on the *absence* of data will be upheld, provided the agency makes a "reasonable predictive judgment." *Prometheus*, 592 U.S. at 427. That is what happened here. FDA reviewed the data, and based on the lack of real-world adverse events and several supporting studies, reasonably predicted that the in-person dispensing requirement could be "modified to reduce the burden on the health care delivery system without

[20] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/021107Orig1s030ltr.pdf.

compromising patient safety." J.A. 394; *see* J.A. 371; 21 U.S.C. § 355-1(f)(2), (g)(4).

Finally, the Fifth Circuit criticized FDA for relying on studies despite "recogniz[ing]" their limitations. Pet. App. 62a. But agency action that candidly acknowledges the "limitations" of its data and "carefully explain[s] why its limited reliance on [that data] was justified" is not arbitrary and capricious. *In re Polar Bear ESA Listing & Section 4(d) Rule Litig.--MDL No. 1993*, 709 F.3d 1, 14 (D.C. Cir. 2013). FDA reasonably identified shortcomings in certain studies and detailed why those studies it *did* rely on, coupled with all the other evidence the agency examined, supported its conclusion that in-person dispensing was not necessary.

C. The Equities Favor Danco.

The Fifth Circuit also erred in analyzing the remaining preliminary-injunction factors. Both the equities and risk of irreparable harm to Danco and the public overwhelmingly favored denying preliminary relief.

The panel's order will cause tremendous harm, including pushing women to later and more invasive surgical abortions or unapproved regimens with more complications, and impeding access to miscarriage management. *E.g.*, Doctors for Am. Cert. Br. 8-11 ("mifepristone means improved access to care" in rural areas); *id.* at 11-16 ("restricting mifepristone would undermine * * * safe and effective management of early pregnancy loss"); ACOG Cert. Br. 5-7, 17-23 (decisions below "compromise patient safety and wellbeing, impede the provision of quality health care services, and threaten the effective functioning of health care institutions and the practice of medicine");

States Cert. Br. 1-3, 8-20 (detailing investments by 23 States and D.C. in medication abortion access); Local Gov'ts Cert. Br. 2, 18-20 (burdens on understaffed and underfunded hospitals); Dr. Goldberg Decl. ¶¶ 9-15 (5th Cir. Apr. 10, 2023), ECF No. 29 (patients "choose medication abortions over surgical ones for many reasons"; limiting access to medication abortion means "patients will carry undesired, high-risk pregnancies forward at great risk to themselves"); Dr. Schreiber Decl. ¶¶ 17-23 (5th Cir. Apr. 10, 2023), ECF No. 29 (medication abortion is often "safer and/or preferable for some patients given their individual circumstances").

The court did not consider the consequences of ordering a less-effective dosing regimen, which would prescribe three times the current recommended amount of mifepristone. And the court did not give any weight to the inevitable gap in access between the effective date of a court order requiring Danco to return to the pre-2016 regime, and the date Danco could begin distributing Mifeprex with "drug labels and documentation that comply with the mifepristone REMS as of 2011." Pet. App. 66a-67a.

The Fifth Circuit's decision also has serious consequences for Danco. The changes required by the injunction are not ones Danco can make quickly or unilaterally—they are major changes that would require Danco to submit an sNDA and for FDA to approve it, even though Danco would be seeking approval for outdated prescribing information and with use conditions that studies repeatedly show are unnecessary. 21 U.S.C. §§ 355(a), (d), 356a; 21 C.F.R. § 314.70(b). The Fifth Circuit never explained how FDA could approve a sort of hypothetical sNDA

effective only upon a decision of this Court to uphold the preliminary injunction, or how FDA could ignore its statutory mandates on safety, efficacy, and the weight of benefits and risk and instead grant a court-ordered sNDA based on that court's concerns. *See* 21 U.S.C. § 355(d). Nor did it address a competing court injunction prohibiting FDA from approving any changes to the 2023 REMS in 17 States and D.C. Order Granting in Part Pls.' Mot. for Prelim. Inj. at 30, *Washington* v. *FDA*, No. 1:23-cv-03026 (E.D. Wash. Apr. 7, 2023), ECF No. 80.

The pharmaceutical industry has offered additional reasons why an injunction here is contrary to the public interest: It would severely destabilize the industry, stifle innovation in drug development, and prevent patients from accessing a drug with a long record of safe and effective use. *See* PhRMA Cert. Br. 19-21; Pharm. Cos. Cert. Br. 12-22. The Fifth Circuit's ruling "represents a destabilizing threat to the investment-backed expectations that make drug innovation possible." PhRMA Cert. Br. 21. And it "threatens a seismic shift in the clinical development and drug approval processes—erecting unnecessary and unscientific barriers to the approval of lifesaving medicines, chilling drug development and investment, threatening patient access, and destabilizing FDA's rigorous, well-established, and longstanding drug approval process." Pharm. Cos. Cert. Br. 22.

CONCLUSION

The judgment of the Fifth Circuit should be reversed and the case remanded with instructions to dismiss for lack of standing. In the alternative, it should be reversed on the merits.

Respectfully submitted,

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