No. 23-10362

In the United States Court of Appeals for the Fifth Circuit

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

Plaintiffs-Appellees

v.

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

Defendants-Appellants

v.

DANCO LABORATORIES, L.L.C.,

Intervenor-Appellant

On Appeal from the United States District Court for the Northern District of Texas, Amarillo Division, Case No. 2:22-cv-00223-Z, Judge Matthew J. Kacsmaryk

OPENING BRIEF FOR INTERVENOR-APPELLANT DANCO LABORATORIES, LLC

PHILIP KATZ
LYNN W. MEHLER
HOGAN LOVELLS US LLP
555 Thirteenth Street, N.W.
Washington, D.C. 20004

EVA M. SCHIFINI
HOGAN LOVELLS US LLP
1999 Avenue of the Stars
Suite 1400
Los Angeles, CA 90067

JESSICA L. ELLSWORTH
CATHERINE E. STETSON
KAITLYN A. GOLDEN
DANIELLE DESAULNIERS STEMPEL
MARLAN GOLDEN
DELIA SCOVILLE
HOGAN LOVELLS US LLP
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5600
jessica.ellsworth@hoganlovells.com

Counsel for Intervenor-Appellant

CERTIFICATE OF INTERESTED PERSONS

The undersigned counsel of record certifies that the following listed persons and entities as described in the fourth sentence of Rule 28.1.1 have an interest in the outcome of this case. These representations are made in order that the judges of this court may evaluate possible disqualification or recusal.

1. Plaintiffs-Appellees:

   Alliance for Hippocratic Medicine

   American Association of Pro-Life Obstetricians & Gynecologists

   American College of Pediatricians

   Christian Medical & Dental Associations

   Shaun Jester, D.O.

   Regina Frost-Clark, M.D.

   Tyler Johnson, D.O.

   George Delgado, M.D.

2. Counsel for Plaintiffs-Appellees:

   Alliance Defending Freedom

   Erik Christopher Baptist

   Denise Harle

   Erica Steinmiller-Perdomo

   Erin Morrow Hawley

   Julie Marie Blake

   Matthew S. Bowman

John J. Bursch

Morgan Williamson LLP

Christian D. Stewart

3. Defendants-Appellants:

U.S. Food and Drug Administration

Robert M. Califf, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration

Janet Woodcock, M.D., in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration

Patrizia Cavazzoni, M.D., in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

U.S. Department of Health and Human Services

Xavier Becerra, in his official capacity as Secretary, U.S. Department of Health and Human Services

4. Counsel for Defendants-Appellants:

U.S. Department of Justice

Elizabeth B. Prelogar

Brian M. Boynton

Leigha Simonton

Sarah E. Harrington

Michael S. Raab

Cynthia A. Barmore

Noah T. Katzen

Christopher A. Eiswerth

Daniel Schwei

Emily Brooke Nestler

Julie Straus Harris

Kate Talmor

5. Intervenor-Appellant:

Danco Laboratories, LLC

Danco Investors Group, LP (Danco Investors Group, LP is 100% owner of Danco Laboratories, LLC)

6. Counsel for Intervenor-Appellant:

Hogan Lovells US LLP

Jessica L. Ellsworth

Catherine E. Stetson

Philip Katz

Lynn W. Mehler

Kaitlyn A. Golden

Danielle Desaulniers Stempel

Marlan Golden

Delia Scoville

Eva M. Schifini

Ryan Brown Attorney at Law

Ryan Patrick Brown

/s/ Jessica L. Ellsworth
Jessica L. Ellsworth

Counsel for Intervenor-Appellant

STATEMENT REGARDING ORAL ARGUMENT

This case concerns far-reaching issues of nationwide importance. Accordingly, this Court has scheduled oral argument for May 17, 2023. *See* ECF No. 191 at 1; ECF No. 193.

TABLE OF CONTENTS

Page

CERTIFICATE OF INTERESTED PERSONS i

STATEMENT REGARDING ORAL ARGUMENT iv

TABLE OF AUTHORITIES vii

INTRODUCTION 1

JURISDICTIONAL STATEMENT 3

ISSUE PRESENTED FOR REVIEW 3

STATUTES AND REGULATIONS 3

STATEMENT OF THE CASE 4

A. Factual Background 4

B. Procedural History 12

SUMMARY OF ARGUMENT 15

STANDARD OF REVIEW 17

ARGUMENT 18

I. THE DISTRICT COURT ERRED IN FINDING PLAINTIFFS LIKELY TO SUCCEED ON THE MERITS 18

A. Plaintiffs' Standing Arguments Are Based On Statistical Possibilities, Depend On Third-Party Discretionary Actions, And Flunk Organizational Standing Prerequisites 18

1. No individual Plaintiff or member of a Plaintiff-Association faces cognizable future injury fairly traceable to FDA's challenged actions 19

2. Plaintiffs lack organizational standing 30

TABLE OF CONTENTS—Continued

3. Plaintiffs lack third-party standing 31

B. Plaintiffs' Challenge To The 2000 Mifeprex Approval Is Time-Barred 32

1. The reopener doctrine does not apply 33

2. Equitable tolling is inapplicable 37

3. Plaintiffs' failure to exhaust is inexcusable 39

C. Plaintiffs' Claims Fail On The Merits 40

1. FDA's 2000 approval and subsequent changes were not arbitrary and capricious 40

2. FDA's initial reliance on Subpart H has no legal effect today, and was permissible in any event 49

D. Plaintiffs' Comstock Act Argument Fails 52

II. THE EQUITIES OVERWHELMINGLY FAVOR DEFENDANTS 56

A. Danco Faces Substantial, Certain, Unrecoverable Harm 56

B. The Public Interest Favors The Government And Danco 58

C. Plaintiffs Face No Irreparable Harm Absent An Injunction 61

CONCLUSION 63

CERTIFICATE OF SERVICE

CERTIFICATE OF COMPLIANCE

ADDENDUM

TABLE OF AUTHORITIES

Page(s)

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Abbott v. Perez,
138 S. Ct. 2305 (2018) 3

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988 F.2d 146 (D.C. Cir. 1993) 50, 61

Ass'n of Am. R.Rs. v. I.C.C.,
846 F.2d 1465 (D.C. Cir. 1988) 35

Attala Cnty., Miss. Branch of NAACP v. Evans,
37 F.4th 1038 (5th Cir. 2022) 28

Atwood Turnkey Drilling, Inc. v. Petroleo Brasileiro, S.A.,
875 F.2d 1174 (5th Cir. 1989) 57

Buffalo Marine Servs. v. United States,
663 F.3d 750 (5th Cir. 2011) 18, 40

Byrum v. Landreth,
566 F.3d 442 (5th Cir. 2009) 17

CAE Integrated, L.L.C. v. Moov Techs.,
44 F.4th 257 (5th Cir. 2022) 17

Cent. & S. W. Servs. v. EPA,
220 F.3d 683 (5th Cir. 2000) 61

Circus Circus Casinos, Inc. v. NLRB,
961 F.3d 469 (D.C. Cir. 2020) 55

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461 U.S. 95 (1983) 19, 25

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568 U.S. 398 (2013) ..... *passim*

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Page(s)

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671 F.3d 1275 (D.C. Cir. 2012).....23

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489 U.S. 561 (1989).....53

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509 U.S. 137 (1993).....32

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325 U.S. 212 (1945).....61

DeNaples v. Off. of Comptroller of Currency,
706 F.3d 481 (D.C. Cir. 2013).....55

Direct Biologics L.L.C. v. McQueen,
63 F.4th 1015 (5th Cir. 2023).....57

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142 S. Ct. 2228 (2022).....60

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41 F.4th 709 (5th Cir. 2022).....*passim*

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982 F.3d 332 (5th Cir. 2020).....30

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141 S. Ct. 1150 (2021).....18, 40, 42, 48

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529 U.S. 120 (2000).....56

Fort Bend County v. U.S. Army Corps of Eng'rs,
59 F.4th 180 (5th Cir. 2023).....51

Greenspan v. Shalala,
38 F.3d 232 (5th Cir. 1994).....18, 40

TABLE OF AUTHORITIES—Continued

Page(s)

Havens Realty Corp. v. Coleman,
455 U.S. 363 (1982).....19, 30

Holmberg v. Armbrecht,
327 U.S. 392 (1946).....62

Hormel v. Helvering,
312 U.S. 552 (1941).....39

Huawei Techs. USA v. F.C.C.,
2 F.4th 421 (5th Cir. 2021).....18, 40

Irwin v. Dep't of Veterans Affs.,
498 U.S. 89 (1990).....38

Kisor v. Wilkie,
139 S. Ct. 2400 (2019).....51

Kowalski v. Tesmer,
543 U.S. 125 (2004).....19, 31, 32

Leocal v. Ashcroft,
543 U.S. 1 (2004).....56

Lujan v. Defenders of Wildlife,
504 U.S. 555 (1992).....20, 28

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544 F.2d 1233 (5th Cir. 1976).....17, 56

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577 U.S. 250 (2016).....38

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670 F.2d 49, 52 (5th Cir. 1982).....52

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626 F.3d 233 (5th Cir. 2010).....30, 31

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Page(s)

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843 F.3d 1010 (D.C. Cir. 2016).....36, 37

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571 F.3d 1245 (D.C. Cir. 2009).....34

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492 F. Supp. 3d 701 (E.D. Tex. 2020).....62

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575 U.S. 92 (2015).....42

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499 U.S. 400 (1991).....19, 31

Pub. Citizen v. Nuclear Regul. Comm'n,
901 F.2d 147 (D.C. Cir. 1990).....37

Serono Lab'ys, Inc. v. Shalala,
158 F.3d 1313 (D.C. Cir. 1998).....44

Sierra Club v. EPA,
551 F.3d 1019 (D.C. Cir. 2008).....33, 34, 35, 36

Summers v. Earth Island Inst.,
555 U.S. 488 (2009).....19, 20, 25, 28

Tenth St. Residential Ass'n v. City of Dallas,
968 F.3d 492 (5th Cir. 2020) 31

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141 S. Ct. 2190 (2021) 19

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712 F.2d 677 (D.C. Cir. 1983) 40

Way of Life Television Network, Inc. v. F.C.C.,
593 F.2d 1356 (D.C. Cir. 1979) 39

STATUTES:

5 U.S.C. § 706(1) ..... *passim*

21 U.S.C. § 331(a) 57

21 U.S.C. § 355 ..... 4, 49

21 U.S.C. § 355(c) 41

21 U.S.C. § 355(d) 41, 45, 55

21 U.S.C. § 355(e) 37

21 U.S.C. § 355-1 49

21 U.S.C. § 355-1(a)(1) 5

21 U.S.C. § 355-1(b)(3) 41

21 U.S.C. § 355-1(f)(2) 41

21 U.S.C. § 355-1(g)(4)(B) 41

21 U.S.C. § 393(b)(1) 56

21 U.S.C. § 505-1 2

28 U.S.C. § 1292(a) 3

28 U.S.C. § 2401(a) 32

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TABLE OF AUTHORITIES—Continued

Page(s)

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§ 506.....21
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§ 909(b)(1) 5, 50
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REGULATIONS:

21 C.F.R. § 10.30(e).....53

21 C.F.R. § 10.45(b) 32

21 C.F.R. § 20.112 47

21 C.F.R. § 314.80 47

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21 C.F.R. § 314.105 4

21 C.F.R. § 314.500 51

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INTRODUCTION

The District Court's unprecedented ruling purports to "stay" FDA's decision in 2000 to approve Mifeprex as safe and effective, and FDA's subsequent actions in 2016 and 2021 modifying the drug's dosing regimen and use restrictions. No court has ever "stayed" the longstanding federal approval of a lawfully marketed drug. Yet the District Court effectively ordered mifepristone off the market—ignoring the substantial evidence supporting FDA's decisions—in a case brought by a group of doctors that neither prescribe the drug nor treat patients seeking medication abortions.

To reach its conclusions, the District Court defied longstanding precedent on Article III standing, timeliness, exhaustion, and administrative procedure. The court found that Plaintiffs demonstrated injury-in-fact by referencing attenuated chains of events involving discretionary acts by third-parties and statistical possibilities that someday, a Plaintiff-physician or some unidentified member of a Plaintiff-Association might (1) encounter the rare woman who needs surgical intervention after a medication abortion *and* seeks care from an emergency room, (2) be required to provide that intervention despite the protections of federal and state conscience laws, and (3) feel aggrieved in doing so. The court's limitations and exhaustion analyses were equally groundless, bending every settled rule to reach stale, unexhausted challenges to agency action.

On the merits, the non-expert court selectively referenced statistical data and admittedly second-guessed FDA's scientific judgments, relying instead on the court's own views and materials post-dating the agency's decisions, such as an analysis of a small number of anonymous blog posts on an anti-abortion website. But even the limited preliminary injunction record makes clear that each challenged FDA action involved careful consideration of available clinical trial data, medical literature, and real-world experience with the drug.

The court also concluded that FDA's 2021 actions violated the 1873 Comstock Act, a criminal statute FDA has no authority to interpret or enforce. And in finding fault with FDA's decision to impose use restrictions through "Subpart H" from 2000-2008, the court disregarded that Mifeprex's use restrictions since 2008 have instead been governed by FDA's statutory REMS[1] authority—not Subpart H.

As for the equities: The court's relentlessly one-sided narrative never mentions the millions of women who have benefitted from the availability of mifepristone or the decidedly non-speculative harms to Danco Laboratories LLC from forcing its only product off the market. The opinion fails to account for harms from forcing women into alternative ways of ending a pregnancy or into carrying an unwanted or unviable pregnancy. It also ignores the destabilizing harm to

[1] Per 21 U.S.C. § 505-1, FDA may condition approval of a drug on the sponsor adopting a Risk Evaluation and Mitigation Strategy (REMS).

innovation facing the pharmaceutical industry if courts can override FDA's considered view of the scientific evidence, invent new rules for drug approvals, and throw out drug approvals based on questionable materials never presented to the agency.

The court's mandatory injunction is an unprecedented judicial assault on a careful regulatory process that has served the public for decades. The injunction should be vacated.

JURISDICTIONAL STATEMENT

This Court has jurisdiction to review the District Court's order, which had "the practical effect of an injunction," under 28 U.S.C. § 1292(a). ROA.4385 & n.3; *see Abbott v. Perez*, 138 S. Ct. 2305, 2319-20 (2018).

ISSUE PRESENTED FOR REVIEW

Whether the District Court erred in issuing a preliminary injunction where Plaintiffs lack standing and their claims are unreviewable and/or fail on the merits; Plaintiffs face no impending harm absent an injunction; and Danco and the public will be irreparably injured by an injunction.

STATUTES AND REGULATIONS

Pertinent statutes and regulations are reprinted in the Addendum.

STATEMENT OF THE CASE

A. Factual Background

In 2000, the Food and Drug Administration (FDA) approved Mifeprex (mifepristone) as safe and effective for use in combination with misoprostol to terminate intrauterine pregnancy through 49 days gestation. ROA.600; *see* 21 U.S.C. § 355; 21 C.F.R. § 314.105. The New Drug Approval (NDA) for Mifeprex, submitted in 1996, presented extensive data on the drug's safety and efficacy, including: data from three clinical trials involving 2,659 women showing mifepristone was effective, meaning further intervention was not required, for 92.1%-95.5% of women; and safety data from a European post-market database of over 620,000 women who had taken mifepristone to terminate a pregnancy. ROA.642-647, 591-598.

In approving Mifeprex as safe and effective, FDA imposed certain use restrictions under 21 C.F.R. § 314.520.[2] ROA.600-601, 596; *see* ROA.376 n.93. An independent review by the U.S. Government Accountability Office (GAO) confirmed that FDA's approval and oversight processes for Mifeprex were consistent with its processes for other drugs with Subpart H use restrictions. GAO,

[2] 21 C.F.R. § 314.520 is part of a set of regulations collectively known as Subpart H, which provides for both imposing use restrictions and accelerating approval for certain new drugs. FDA invoked Subpart H in its review of mifepristone solely for the use restrictions. *See* ROA.596.

GAO-08-751, *FDA: Approval and Oversight of the Drug Mifeprex* (Aug. 2008), https://www.gao.gov/assets/gao-08-751.pdf.

In 2002, some of the Plaintiffs filed a citizen petition with FDA asserting that Mifeprex was improperly approved under Subpart H and is not safe and effective as approved. ROA.354-444. FDA ultimately denied the petition in March 2016, meticulously documenting and reaffirming that medication abortion is safe and effective and provides a meaningful therapeutic benefit over surgical abortion for many patients. ROA.635-667. Plaintiffs could have filed suit to compel FDA to act on their pending petition at virtually any point during that 14-year period. *See* 5 U.S.C. § 706(1). They never did.

In 2007, Congress amended the Food, Drug, and Cosmetic Act (FDCA) to provide statutory authority for FDA to impose certain restrictions on drugs in the form of a Risk Evaluation and Mitigation Strategy (REMS) when necessary "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1(a)(1). Congress "deemed" drugs previously approved with use restrictions through Subpart H to have a REMS in effect while the sponsors submitted supplements to their approved applications to include a REMS. FDA Amends. Act of 2007, Pub. L. 110-85, §§ 909(b)(1), (3), 121 Stat. 823 (2007); *see* Identification of Drug and Biological Products, 73 Fed. Reg. 16313 (Mar. 27, 2008). FDA

approved Danco's sNDA with a REMS in June 2011. ROA.672. Mifeprex's approval today is governed by FDA's REMS authority.

In 2015, Danco submitted a supplemental New Drug Approval (sNDA) to modify certain aspects of Mifeprex's indication and dosing regimen, also implicating the REMS. Among other things, it sought to: (1) lower the mifepristone dose from 600 mg to 200 mg and increase the misoprostol dose from 400 mcg to 800 mcg, to be administered in the cheek pouch for slower absorption; (2) extend the approved gestational age from 49 to 70 days; (3) allow administration of misoprostol at home; (4) allow follow up other than through an in-clinic appointment; and (5) allow prescribing by certified healthcare providers licensed under state law. Danco submitted extensive data reflecting fifteen years of experience with the drug and more than twenty clinical studies addressing various changes sought in the sNDA. ROA.689-696, 703-715, 2170-2174.

In reviewing the proposed dosing regimen and gestational age changes, FDA compiled a summary of relevant U.S. clinical studies involving 16,794 patients:

Clinical Review
(b) (6) and (b) (6)
NDA 020687/S-020- Mifeprex

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.

ROA.2171.

It similarly compiled a summary of non-U.S. studies involving 18,425 patients:

Clinical Review
(b) (6) and (b) (6)
NDA 020687/S-020- Mifeprex

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.

ROA.2172-2173.

As an FDA reviewer explained, the success rates for medication abortion in these studies were "97.4% (US) and 96.1% (non-US)," which "strongly support the

proposed new dosing regimen and the extension of the acceptable gestational age." ROA.2173.

FDA also carefully analyzed the literature for information about adverse events. One study that found only "29 women of 13,221 (0.1%) undergoing medical abortion experienced a major complication," meaning "emergency department presentation, hospitalization, infection, perforation and hemorrhage requiring transfusion;" another found only 4 of 1,172 patients (0.3%) prescribed a medication abortion through telemedicine required a blood transfusion, compared to 0.1% of 2,384 in-person patients; and a third found tiny numbers (0-0.5%) of hospitalizations, serious infections, or blood transfusions through 70 days gestation. ROA.2198. These (and others) showed serious adverse events from the proposed regimen were "rare," "generally far below 1.0% for any individual adverse event." ROA.2198; *see also* ROA.2198-2199 (discussing study demonstrating "no higher" incidence of "[s]erious fatal or nonfatal adverse events in the 64-70 days gestation group" and concluding "[b]ased on the available safety data on medical abortion in totality, it appears that serious fatal or nonfatal adverse events are very rare through 70 days").

FDA also "comprehensive[ly] review[ed]" "adverse events associated with Mifeprex from September 28, 2000 through November 17, 2015." ROA.2224. For that 15-year period, providers were required to report all serious adverse events

associated with Mifeprex. ROA.2150. As the following table summarizing this data shows, of the more than 2.5 million women who had taken mifepristone, fewer than one-tenth of one percent experienced *any* adverse event; far fewer experienced the other listed adverse events; and only 878 women out of the more than 2.5 million who had taken mifepristone—0.035%—were hospitalized.

Table 21: US Postmarketing AEs- Mifepristone for Medical Abortion

Date ranges of reports received	09/28/00[†]-10/31/12	11/1/12 - 04/30/14[‡]
Cases with any adverse event	2740	504
Hospitalized, excluding deaths	768	110
*Experienced blood loss requiring transfusions[§]	416	66
Infections[‖] (*Severe infections[¶])	308 (57)	37 (5)

[†] U.S. approval date.
[‡] FDA implemented FAERS on September 10, 2012, and migrated all of the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. As a result of this change, it is not recommended to calculate a cumulative number when reviewing the data provided in Table 5.
[*] The majority of these women are included in the hospitalized category in Table 5.
[§] As stated in the approved Mifeprex (mifepristone) labeling, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days. Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.
[‖] This category includes endometritis (inflammation resulting from an infection involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as chlamydia and gonorrhea, cystitis, and toxic shock syndrome not associated with a pelvic infection.
[¶] This subset of infections includes cases that were determined to be severe based on medical review of the available case details. Severe infections generally result in death or hospitalization for at least 2-3 days, require intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, or have other physical or clinical findings, laboratory data, or surgery that suggest a severe infection.

Source: Review by (b) (6) (b) (6) (b) (6) dated 08/27/2015.

ROA.2225-2226. From all these data and more, the FDA reviewer concluded that the proposed changes would not unacceptably increase "the numbers of

hospitalizations, severe infections, blood loss requiring transfusion and ectopic pregnancy" occurrences. ROA.2226.

FDA approved these changes in 2016. ROA.689-696. GAO again found this approval process followed FDA's standard procedures. *See* GAO, GAO-18-292, *FDA: Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts* (Mar. 2018), https://www.gao.gov/assets/gao-18-292.pdf.

In 2019, FDA approved a generic version of mifepristone. Also in 2019, some of the Plaintiffs filed a citizen petition asking FDA to rescind certain of the 2016 changes and to "retain the Mifeprex [REMS]" that had been in place since 2011. ROA.741. The 2019 petition did not ask FDA to rescind Mifeprex's 2000 approval.

In April 2021, FDA announced it would temporarily exercise enforcement discretion with respect to in-person dispensing during the COVID-19 pandemic. ROA.787-788. FDA's decision was based on medical literature relevant to modifying this requirement, postmarketing adverse events from earlier in the pandemic, and available information about deviations or noncompliance events associated with the REMS. ROA.787-788; *see also* ROA.827-829.

In December 2021, FDA largely denied the 2019 citizen petition. It thoroughly explained its decision to keep the 2016 REMS in place and to continue exercising enforcement discretion with respect to the in-person dispensing

requirement. *See* ROA.803-842. FDA granted the 2019 petition insofar as it asked FDA to "retain" the Mifeprex REMS, rather than remove them entirely. ROA.826.

On January 3, 2023, FDA approved a June 2022 sNDA to modify the mifepristone REMS and lift the in-person dispensing requirement. Plaintiffs did not amend their complaint or otherwise challenge this approval.

B. Procedural History

1. In November 2022, Plaintiffs filed suit under the Administrative Procedure Act (APA) challenging FDA's 2000 Mifeprex approval, 2002 citizen petition denial, 2016 REMS changes, 2019 generic approval, 2021 citizen petition denial, and 2021 non-enforcement decision. Plaintiffs moved for a preliminary injunction. ROA.1027-1031. Danco intervened. In opposing Plaintiffs' motion, Danco identified several fundamental threshold problems, including standing, timeliness, and administrative exhaustion. On the merits, Danco explained that all of FDA's challenged actions were supported by meticulous reasoning and rafts of data. Danco also explained that Plaintiffs' contentions of irreparable harm absent an injunction rang false, given Plaintiffs' leisurely approach to bringing suit.

All parties supported the District Court considering the full administrative record before reaching a decision on the merits. ROA.3240-3252, 3588-3596, 3801-3811. Instead, the court opted to rely on the preliminary injunction record alone, ROA.4192, and granted Plaintiffs' request for preliminary relief. ROA.4373.

The District Court first concluded Plaintiffs had standing, could surmount a number of reviewability issues, and were likely to prevail on the merits. The court found standing because (1) adverse events from medication abortion can "overwhelm the medical system," place "pressure and stress" on doctors, prevent Plaintiffs "from practicing evidence-based medicine," and increase risks of malpractice allegations; (2) third-party standing applied; and (3) the Plaintiff-Associations had suffered a "diversionary injury." ROA.4313-4319 (quotation marks omitted).

On statute of limitations, the court excused Plaintiffs' decision to file suit eight months after the six-year limitations period expired on the basis that FDA had taken too long to respond to the 2002 citizen petition—even though the limitations period did not start until FDA *did* respond. The court similarly excused exhaustion for several of Plaintiffs' claims. ROA.4333-4334, 4336-4337. And the court seized upon one reference to a "full review" of the REMS, ROA.808, to opine that FDA must have "reopened" in 2021 the question whether to withdraw mifepristone's 2000 approval. ROA.4328-4329.

On the merits, the court disagreed with FDA's use of Subpart H in approving mifepristone, and held FDA's subsequent actions arbitrary and capricious. ROA.4355-4366. The court largely failed to engage with FDA's actual decisionmaking, instead relying on materials post-dating the agency's decisions and

the court's own research. The court also invoked the Comstock Act as a reason to enjoin FDA's 2021 non-enforcement decision. ROA.4338-4344.

On irreparable harm, the court held that "time" treating patients and "mental and monetary costs" for doctors was irreparable. ROA.4367 (quotation omitted). As for the balance-of-harms and public-interest factors, the court ignored the vast majority of women for whom medication abortion has been, and will continue to be, a complete and medically appropriate treatment, as well as the concrete and irreparable financial harm to Danco from ordering its only product removed from the market.

Finally, the court purported to "stay" FDA's 2000 approval of Mifeprex, characterizing its decision upending 23 years of FDA approval as just maintaining the status quo. ROA.4370-4373. The court ignored both the heightened mandatory injunction standard and the possibility of remand *without* vacatur even in the event Plaintiffs prevailed on the merits.

2. Danco and the Government sought a stay pending appeal. ECF Nos. 20, 22.[3] Plaintiffs opposed and sought dismissal of the appeals on jurisdictional grounds. ECF No. 98.

[3] Unless otherwise specified, ECF references are to this Fifth Circuit docket, No. 23-10362. ECF page numbers reference the ECF header.

This Court denied Plaintiffs' motion to dismiss, ROA.4385 n.3, and partially stayed the District Court's order.[4] The panel majority stayed the injunction as to FDA's 2000 approval, agreeing that Plaintiffs' challenge was likely untimely. ROA.4379-4419. It left the injunction in effect as to FDA's 2016 REMS modifications and 2021 non-enforcement decision. ROA.4419.

Danco and the Government applied to the Supreme Court for a stay. The Supreme Court granted those applications on April 21, 2023. Order, *Danco Labs. v. All. for Hippocratic Med.*, No. 22A901 (U.S. Apr. 21, 2023). Only two Justices noted disagreement with granting the stay applications. *Id.*

SUMMARY OF ARGUMENT

I. The District Court erred on multiple grounds in holding that Plaintiffs were likely to succeed on the merits. Plaintiffs lack individual, associational, or organizational standing to challenge FDA's approvals of a drug they do not prescribe that is the standard of care for patients seeking a medical procedure they do not provide. No Plaintiff faces a "certainly impending" cognizable injury fairly traceable to any challenged FDA action, and no Plaintiff-Association has changed its anti-abortion activities on account of any challenged actions.

[4] Judge Haynes concurred only in expediting the appeals and denying the motion to dismiss. She would have granted an administrative stay and deferred whether to stay the District Court's order to the merits panel. ROA.4379 n.*.

Plaintiffs' challenge to FDA's 2000 approval is time-barred, as the stay panel rightly concluded. The six-year clock to challenge FDA's March 2016 denial of their citizen petition expired eight months before they filed suit. And Plaintiffs failed to exhaust certain of their claims to boot.

Beyond these several fundamental threshold deficiencies, Plaintiffs' substantive arguments run headlong into black-letter APA law prohibiting courts from invoking their own views rather than reviewing whether FDA reasonably exercised its expert judgment and whether substantial evidence supports FDA's finding of safety and efficacy. Their Subpart H argument has no legal consequence today and is wrong in any event. And their unexhausted Comstock Act-based challenge ignores the scope and limits of FDA's statutory mandate.

II. The District Court's analysis of the equities was also flawed. The court entirely failed to acknowledge the harm to Danco from blocking its only product from the market. The District Court also failed to weigh the harms to the many women who rely on mifepristone, including the overwhelming majority of women for whom medication abortion is a complete treatment. On top of that, enjoining a longstanding drug approval based on judicial second-guessing of FDA's scientific expertise will destabilize the pharmaceutical industry; impose high costs on the healthcare system, including by limiting provider availability for other patient care; negatively impact providers, cities, and states; and raise separation-of-powers

concerns. No Plaintiff, by contrast, faces irreparable harm absent an injunction. If the rare possibility arises in which a woman, after a medication abortion, requires follow-up care and seeks it from a facility where one of the Plaintiff-physicians works, federal and state conscience laws protect Plaintiffs' rights not to provide surgical abortion care.

STANDARD OF REVIEW

A preliminary injunction is "an extraordinary remedy" that requires a moving party to "clearly" show: "(1) a substantial likelihood of success on the merits," (2) irreparable injury absent an injunction, (3) "that the injury outweighs any harm to" other parties, and (4) that "the injunction will not disserve the public interest." *CAE Integrated, L.L.C. v. Moov Techs.*, 44 F.4th 257, 261 (5th Cir. 2022). That burden increases when the preliminary injunction is mandatory: A mandatory injunction changing the status quo "is particularly disfavored, and should not be issued unless the facts and law clearly favor the moving party." *Martinez v. Mathews*, 544 F.2d 1233, 1243 (5th Cir. 1976). Although the ultimate grant of a preliminary injunction is reviewed for abuse of discretion, "a decision grounded in erroneous legal principles is reviewed *de novo*." *Byrum v. Landreth*, 566 F.3d 442, 445 (5th Cir. 2009) (quotation omitted).

Courts review agency action under the APA using the familiar arbitrary-and-capricious standard. To survive this "narrow and highly deferential" standard,

Huawei Techs. USA v. F.C.C., 2 F.4th 421, 449 (5th Cir. 2021) (quotation omitted), the agency's actions need only be "reasonable and reasonably explained," *F.C.C. v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021). The agency's factual findings are reviewed for substantial evidence. *Buffalo Marine Servs. v. United States*, 663 F.3d 750, 753-754 (5th Cir. 2011). Reviewing courts "may not reweigh the evidence, try the issues *de novo*, or substitute [their] judgment for" the agency's. *Greenspan v. Shalala*, 38 F.3d 232, 236 (5th Cir. 1994).

ARGUMENT

I. THE DISTRICT COURT ERRED IN FINDING PLAINTIFFS LIKELY TO SUCCEED ON THE MERITS.

A. Plaintiffs' Standing Arguments Are Based On Statistical Possibilities, Depend On Third-Party Discretionary Actions, And Flunk Organizational Standing Prerequisites.

Plaintiffs assert they have standing because some Plaintiff-physician or Plaintiff-Association member doctor might be asked to treat an unidentified patient in some emergency room on some unknown future date for a rare complication stemming from a drug some other provider prescribed, which is the standard of care for a medical practice no Plaintiff-physician performs. That daisy-chain of speculation alleges nowhere close to a "substantial risk" of "certainly impending" harm. *Clapper v. Amnesty Int'l, USA*, 568 U.S. 398, 414 n.5 (2013) (quotations omitted). It is instead "equal parts sweeping and unprecedented." *E.T. v. Paxton*, 41 F.4th 709, 722 (5th Cir. 2022).

Plaintiffs' theory, and the District Court's acceptance of it, cannot be squared with Supreme Court precedent on injury-in-fact, causation, or redressability. *See Clapper*, 568 U.S. at 409; *Summers v. Earth Island Inst.*, 555 U.S. 488, 492-493 (2009); *City of Los Angeles v. Lyons*, 461 U.S. 95, 101-102 (1983). Supreme Court precedent also requires organizational plaintiffs to satisfy all the same requirements as individuals. *E.g.*, *Summers*, 555 U.S. at 497-498; *Havens Realty Corp. v. Coleman*, 455 U.S. 363, 378-379 (1982). And it limits third-party standing to circumstances in which plaintiffs can show their own standing, *Powers v. Ohio*, 499 U.S. 400, 410-411 (1991), "a 'close' relationship" to the party on whose behalf they claim to sue, and "a 'hindrance' to [that third party's] ability to protect his own interests." *Kowalski v. Tesmer*, 543 U.S. 125, 130 (2004) (citations omitted).

Applying these straightforward principles, Plaintiffs cannot establish standing.

1. No individual Plaintiff or member of a Plaintiff-Association faces cognizable future injury fairly traceable to FDA's challenged actions.

In *TransUnion L.L.C. v. Ramirez*, 141 S. Ct. 2190 (2021), the Supreme Court admonished that Article III requires plaintiffs to "demonstrate standing for each claim that they press and for each form of relief that they seek," *id*. at 2208, by showing a "sufficiently imminent and substantial" injury, *id*. at 2210. That means

Plaintiffs must establish injury-in-fact, causation, and redressability for each FDA action they challenged. They cannot do so for any of them.

Ample precedent establishes that Plaintiffs may not access a federal court with speculative theories of injury. In *Clapper*, the Supreme Court held that attorneys, human rights organizations, and media organizations lacked standing because their theory of injury—that their communications with clients and contacts would be intercepted by the Government—"rel[ied] on a highly attenuated chain of possibilities" and "speculation about 'the unfettered choices made by independent actors not before the court.'" 568 U.S. at 410, 414 n.5 (quoting *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 562 (1992)). An "objectively reasonable likelihood" that plaintiffs might be harmed in the future was not enough. *Id.* at 410. The Court held that plaintiffs seeking injunctive relief must demonstrate "th[e] threatened injury" they allege is "certainly impending." *Id*. at 409 (quotations omitted). Likewise, in *Summers*, the Supreme Court held environmental organizations lacked standing to challenge regulations that "neither require[d] nor forb[ade] any action on the part of respondents," 555 U.S. at 493, and that showing past harm to a few organization members was insufficient for injunctive relief, even when coupled with "a statistical probability that some [members] are threatened with concrete injury." *Id*. at 495; *accord, e.g.*, *E.T.*, 41 F.4th at 715.

These cases doom Plaintiffs' claims. Plaintiffs have not identified any "certainly impending" future injury arising out of FDA's 2000 approval, or the 2016 or 2021 changes. The individual Plaintiff-physicians oppose abortion. They do not prescribe medication abortion, consult on elective abortions, or perform surgical abortions as part of their regular practice. Nor are they required to do so by any FDA action challenged in this case or by any other federal law. No Plaintiff-physician seeks to treat patients who have had medication abortions—the opposite appears to be true. In the world of physicians who could or would possibly treat a woman for any medical reason associated with a medication abortion, these doctors are among the very last to be considered.

Neither Plaintiffs nor the District Court dispute any of this. Instead, Plaintiffs' theorize that some other provider will prescribe mifepristone to a patient who wants a medication abortion; that patient will experience a rare incomplete abortion, an even rarer "complication," or a yet-rarer-still serious adverse event; instead of seeking follow-up care with their provider (or at that provider's practice), the patient will go to the emergency room; a Plaintiff-physician will be on staff; and that Plaintiff-physician will be *required* to treat that patient, despite federal and state laws that protect a doctor's right to decline to provide medical services to which they have a conscience objection. *See, e.g.*, 42 U.S.C. §§ 238n, 300a-7(c) & 7(d); Consolidated Appropriations Act 2022, Pub. L. No. 117-103, tit. V, §§ 506-507, 136 Stat. 49;

Nadia N. Sawicki, *Protections from Civil Liability in State Abortion Conscience Laws*, 322 JAMA 1918, 1918 (2019); Tex. Occ. Code Ann. § 103.001 (1999) ("A physician … who objects to directly or indirectly performing or participating in an abortion procedure may not be required to directly or indirectly perform or participate in the procedure.").

That highly speculative chain of events depends heavily on the actions of third-parties—just like the standing theories rejected in *Clapper* and *Lujan*. The District Court did not even attempt to apply these precedents, or others like them, to Plaintiffs' claims. ROA.4313-4314 (citing one unpublished case in discussing individual injury). Instead, the District Court invented a new standing superdoctrine just for doctors. And the stay panel, for its part, engaged in some statistical wizardry to find standing where none exists.

The new "doctor standing" superdoctrine. The District Court transformed the daily realities of medical work in an emergency room into an Article III injury. ROA.4313. A doctor's job is to treat patients—which may involve "'pressure and stress,'" or require "'time and attention.'" ROA.4313 (quoting ROA.1048). Those demands are not cognizable injuries: They are facts of the medical profession, especially in emergency rooms. If doctors could sue any time their workload or stress increased because they treated a patient, they would have Article III standing to challenge any product, activity, or regulation that caused someone to seek

treatment from them—from handguns to pollution to cars. The "limitlessness" of that theory illustrates why it is not the law. *E.T.*, 41 F.4th at 721-722 (rejecting similarly unbounded standing theory).

The emotional discomfort associated with providing voluntary medical care to a person with whom a physician has a moral, ethical, or religious disagreement is likewise not an Article III injury. ROA.4313-4314. FDA does not mandate Plaintiffs prescribe mifepristone to anyone, or that Plaintiffs treat patients who have requested and been prescribed mifepristone by others. ROA.1748. Nor could it. *See supra* pp. 21-22 (citing conscience statutes). Where, as here, "FDA is not forcing" a doctor to administer a particular treatment, or "forcing any patient to receive such" treatment, the fact that FDA permits another doctor to prescribe a treatment to patients who seek it does not create standing for one who finds the treatment objectionable. *Coal. for Mercury-Free Drugs v. Sebelius*, 671 F.3d 1275, 1281 (D.C. Cir. 2012) (Kavanaugh, J.).[5]

Nor has any Plaintiff personally suffered past harm on those bases, or any other. The District Court and stay panel rewrote what declarants said "may," "could," or "might" happen into conclusions that such things *did* happen, *compare* ROA.4313-4314 ("These emergencies force doctors into situations 'in which they

[5] Plaintiffs' asserted fear of increased medical liability is equally groundless. No declarant provided any facts about increased liability.

feel complicit in the elective chemical abortion'" (citation omitted)), *with, e.g.*, ROA.282 (FDA's actions "*could* force me to have to [perform an abortion]" (emphasis added)); misquoted declarations to attribute surgical abortions performed by *other doctors* to an individual Plaintiff, *compare* ROA.4390, *with* ROA.268-269 (colleague performed abortion)[6]; ROA.278 (no statement that Plaintiff performed surgical abortion for any patient); ROA.279 ("the doctors"—not Plaintiff—"finish[ed] the abortion"); and cited declarations not asserting a conscience injury, *compare* ROA.4391-4392, *with* ROA.957-962 (no conscience injury); ROA.279 (no assertion declarant had to perform procedure against her will). Plaintiffs also failed to link any purported past injury to the 2016 and 2021 changes, or even identify if the events happened before or after those changes. *E.g.*, ROA.268, 277-279.

Moreover, under *Clapper*, a plaintiff must do more than demonstrate an "objectively reasonable likelihood" of future harm to satisfy "the well-established … 'certainly impending' requirement." 568 U.S. at 401 (quotation omitted). Where a statute "at most authorizes—but does not mandate or direct"—a particular action, alleging harm from an independent actor's discretionary decision is "necessarily conjectural." *Id.* at 412; *accord E.T.*, 41 F.4th at 721.

[6] Indeed, most circumstances described involve care that was provided by *other doctors*, not declarants. *E.g.*, ROA.269, 279.

The District Court purported to "distinguish" *Clapper*'s future-injury requirement on the basis that Plaintiffs demonstrated past harm. ROA.4320. They did not, *see supra* pp. 23-24, but in any event, *past* incidents are no substitute for personal, concrete, impending *future* injury to a specific plaintiff. *Summers*, 555 U.S. at 495; *Lyons*, 461 U.S. at 103. Plaintiff-physicians' statements that they—or someone they know—previously treated a woman for medication-abortion-related complications cannot excuse their failure to show a sufficiently imminent, non-speculative personal risk of future harm. *See Clapper*, 568 U.S. at 409.

The stay panel's unsupportable statistical analysis. The stay panel's different—but equally flawed—reasoning in analyzing Plaintiffs' future injury from FDA's 2016 and 2021 actions underscores the impropriety of basing standing on statistical possibilities.

The panel reasoned that because the Mifeprex label says treatment may be "unsuccessful" in 2-7% of women, ROA.4389, the 5 million women who have used mifepristone over the past 23 years may have included up to 350,000 women who needed additional care to terminate their pregnancy.

That breezy math doesn't add up to standing. First, this calculation bears no connection to how many women have sought *emergency room care* as opposed to a follow-up surgical abortion with their provider, or an additional dose of misoprostol. The stay panel misread the Patient Agreement form to say that patients "must …

seek 'emergency care,'" ROA.4390, but the form actually directs patients to confer with the prescribing "healthcare provider," ROA.4389. And the data belies any assumption that women exclusively seek emergency care: In 15 years of mandatory provider reporting, only 878 out of more than 2.5 million women were hospitalized (0.035%). ROA.2225; *see* ROA.715.

The stay panel's calculation also bears no causal connection to *FDA's 2016 or 2021 actions*. The standing question at issue with respect to Plaintiffs' claims as to those actions is whether any Plaintiff-physician imminently faces being forced to provide a surgical abortion *because of those FDA actions*. There was no such showing, and the panel reached no such conclusion.

Second, the small percentage of women who have experienced an incomplete treatment in no way links up to any Plaintiff-physician: Taking the panel's high-end number (350,000) at face value, dividing it across 23 years, and the number of U.S. emergency rooms (roughly 6,000) and urgent care centers (roughly 9,000), means each facility treated approximately one woman per year—and only assuming not one patient returned to the clinic or provider who prescribed the medication initially.

Whatever "certainly impending" is, it is more than a fraction of a fraction of a percentage of possibility.[7]

Third, the *likelihood* that any Plaintiff would encounter such a woman cuts the fraction down further. In concluding that a Plaintiff-Association member would "inevitabl[y]" treat one of these women "in the future," the stay panel assumed that *every single member* is an emergency room doctor. ROA.4394. That is unreasonable. One association is the American College of *Pediatricians*, an association of "physicians and other healthcare professionals" "dedicated to the well-being of children," Am. Coll. of Pediatricians, *Frequently Asked Questions*, https://acpeds.org/about/faq (last visited Apr. 26, 2023); another is the Christian Medical and *Dental* Association, whose member search function lists only 59 "Emergency Medicine" physicians, *see* Christian Med. & Dental Ass'n, *Christian Healthcare Professional Search*, https://cmda.org/member-search/ (last visited Apr. 26, 2023); and the American Association of Pro-Life Obstetricians and Gynecologists is open to retired physicians, non-physicians, and non-medical individuals, among others, *see* AAPLOG, *Join AAPLOG Today!*,

[7] *See* Jonathan Adler, *The Good and Bad of the Fifth Circuit's Abortion Pill Ruling*, reason.com (Apr. 13, 2023), https://reason.com/volokh/2023/04/13/the-good-and-bad-of-the-fifth-circuits-abortion-pill-ruling/.

https://aaplog.org/become-a-member/ (last visited Apr. 26, 2023).[8] No facts in the record show how many Plaintiff-Association members are emergency room doctors who treat patients like these hypothetical women.

As *Summers* held, finding standing based on such statistical probabilities would "make a mockery" of Article III. 555 U.S. at 498-499; *see also Lujan*, 504 U.S. at 567 (standing may not be rooted in "pure speculation and fantasy"); *E.T.*, 41 F.4th at 715 ("This circuit does not recognize the concept of probabilistic standing based on a non-particularized increased risk." (quotation omitted)); *Attala Cnty., Miss. Branch of NAACP v. Evans*, 37 F.4th 1038, 1043 (5th Cir. 2022) (no standing absent facts showing "a 'real and immediate threat' or a 'substantial risk' that all those events" required for future injury to come to fruition "will occur to one of them").

The District Court nevertheless asserted that "Plaintiffs have good reasons to believe their alleged injuries will continue in the future." ROA.4321. In particular, the District Court credited Plaintiffs' argument that eliminating the mandatory, additional provider adverse-event reporting requirement "radically altered the standard of care" for certified prescribers and "harms the doctor-patient relationship"

[8] *See also* Adam Unikowsky, *Mifepristone and the Rule of Law, Part III* (Apr. 13, 2023), https://adamunikowsky.substack.com/p/mifepristone-and-the-rule-of-law-f6a (detailing erroneous assumptions in the stay panel's analysis).

because Plaintiffs can no longer obtain "informed consent." ROA.4314-4315 (quotation omitted). But mifepristone is still subject to heightened adverse-event reporting requirements. *See infra* p. 47. And no Plaintiff-doctor has ever sought informed consent for medication abortion; *they do not prescribe mifepristone to anyone*. That is true regardless of what FDA does or does not require of healthcare providers who *are* certified to prescribe the drug.

Meanwhile, the stay panel focused on Plaintiffs' baseless claim that the 2016 changes would increase the risk of complications from ectopic pregnancies. ROA.4392-4393. Again, no facts in any standing declaration support this concern: No Plaintiff identified ever treating a woman with an ectopic pregnancy after she took mifepristone, let alone as a result of the 2016 REMS changes. Plaintiffs' declarations instead offered vague, conclusory statements with no basis in personal experience and no factual link to the 2016 and 2021 changes. *Compare* ROA.4321 (declarant expressed concern that injuries may occur "*possibly* with greater frequency than in the past") (emphasis added), *with, e.g.*, ROA.788 (FDA analysis of studies showing no increased safety concerns with non-enforcement of in-person dispensing); ROA.842 (FDA concluding that "[w]e have not identified any new safety concerns with the use of mifepristone for this indication"); ROA.827-837 (reviewing assessment data, postmarketing safety information, and published medical literature); *see also* ROA.813-814 (reiterating unchanged requirement that

certified prescribers must be able to accurately "assess the duration of the pregnancy" and "diagnose ectopic pregnancies"); ROA.817 (reducing number of in-person follow-ups "does not compromise patient safety"). The District Court's "remarkable" decision to "excuse plaintiffs from showing such proof" of *actual* future injury traceable to *any* action on the part of FDA "squarely conflicts with the precedents described above." *E.T.*, 41 F.4th at 716.

2. Plaintiffs lack organizational standing.

The District Court's conclusion that organizational standing exists based on a "diversionary injury" similarly fails to square Plaintiffs' allegations with the law's requirements. ROA.4318-4319. "[A]n organization does not automatically suffer a cognizable injury in fact by diverting resources in response to a defendant's conduct." *El Paso County v. Trump*, 982 F.3d 332, 343 (5th Cir. 2020). Rather, the alleged "diversion" must *also* significantly and "perceptibly impair[]" the organization's mission, and have a "consequent drain on the organization's resources." *Havens*, 455 U.S. at 379; *accord NAACP v. City of Kyle*, 626 F.3d 233, 238 (5th Cir. 2010). A "simpl[e] … setback to the organization's abstract social interests," *Havens*, 455 U.S. at 379, or conduct that does not "differ from [the organization's] routine activities" will not suffice. *El Paso County*, 982 F.3d at 344.

Challenging FDA's actions has not "perceptibly impair[ed]" Plaintiff-Associations' broader goals; it *is* their goal. *E.g.*, ROA.232 ("CMA and its members

are morally and ethically opposed to all forms of abortion"); ROA.252 ("CMDA is opposed to elective abortions"); ROA.266 ("AAPLOG and its members oppose elective abortions"). Indeed, the only specific injury the District Court identified fits into the associations' conceded "duties and responsibilities." *Compare* ROA.4319 (holding that "educating" members about "dangers" of medication abortion constitutes diversionary injury), *with* ROA.231-232, 235, 240-242. And because these organizations have opposed medication abortion "for decades," ROA.1046, their actions did not arise after, and because of, FDA's 2016 or 2021 actions. The absence of a "causal connection between the injury and the conduct complained of" precludes organizational standing. *City of Kyle*, 626 F.3d at 237; *Tenth St. Residential Ass'n v. City of Dallas*, 968 F.3d 492, 499 (5th Cir. 2020).

3. Plaintiffs lack third-party standing.

The District Court also stretched third-party standing—a theory "not looked favorably upon" to begin with—past its breaking point. *Kowalski*, 543 U.S. at 130. Third-party standing first requires proving individual standing, *see Powers*, 499 U.S. at 410-411, which Plaintiffs have not done. It also requires "a 'close' relationship" and a "'hindrance' to the possessor's ability to protect his own interests," *Kowalski*, 543 U.S. at 130 (citations omitted), neither of which are present here.

Plaintiff-physicians lack a close relationship with patients who want an abortion and were prescribed mifepristone by another doctor. Their "relationship"

is at worst antagonistic, and at best nonexistent. *Id.* at 131 ("no relationship" means no third-party standing). Plaintiffs acknowledged as much in their declarations. *E.g.*, ROA.289 ("physicians must treat women … without an existing relationship with the patient"); ROA.233 ("[E]mergency department doctors do not have a prior relationship with these patients …."). Moreover, third-party standing cannot be based on a relationship with a "hypothetical" future patient. *See Kowalski*, 543 U.S. at 131. And Plaintiffs offer no facts showing any patient is hindered in bringing suit.

B. Plaintiffs' Challenge To The 2000 Mifeprex Approval Is Time-Barred.

Plaintiffs' challenge to the 2000 approval is untimely. The stay panel majority correctly concluded as much. ROA.4401-4407. FDA denied Plaintiffs' 2002 citizen petition in March 2016. Plaintiffs had six years from then to sue. *See* 28 U.S.C. § 2401(a). Plaintiffs filed suit six years and eight months later. ROA.185.

Plaintiffs have not and cannot argue that their 2019 citizen petition revives a challenge to the 2000 approval. The 2019 petition actually urged FDA to "*restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000*." ROA.741 (emphasis added). It contains no challenge to the 2000 approval. *See* 21 C.F.R. § 10.45(b); *Darby v. Cisneros*, 509 U.S. 137, 153 (1993).

The District Court proffered two theories for why it could nevertheless review this time-barred claim: reopener or equitable tolling. And despite finding Plaintiffs'

challenge untimely, the stay panel majority suggested that Plaintiffs' failure to exhaust their challenge to the 2000 approval in the 2019 petition was excusable. All three of those conclusions are wrong.

1. The reopener doctrine does not apply.

"The reopener doctrine allows judicial review where an agency has—either explicitly or implicitly—undertaken to 'reexamine its former choice.'" *Nat'l Mining Ass'n v. U.S. Dep't of Interior*, 70 F.3d 1345, 1351 (D.C. Cir. 1995) (citation omitted). An agency "actual[ly]" reopens a prior decision by holding out the existing decision "as a proposed regulation" and soliciting and responding to comments in re-examining the existing regulation. *Sierra Club v. EPA*, 551 F.3d 1019, 1024 (D.C. Cir. 2008) (quotation omitted). An agency can also "constructively reopen a rule" if its later decision "significantly alters the stakes of judicial review." *Id.* at 1025 (quotations and brackets omitted).

The District Court appeared to find reopener because (1) FDA "significantly departed from the agency's original approval" of mifepristone in 2016 and 2021, and (2) FDA's 2021 petition denial stated FDA had conducted a "full review" of the mifepristone REMS, which must have meant FDA "necessarily consider[ed] the possibility that a drug is too dangerous to be on the market." ROA.4328. Neither rationale supports reopener.

Nothing in the 2016 or 2021 changes shows that FDA explicitly or implicitly reexamined its 2000 conclusion that mifepristone was safe and effective for use in combination with misoprostol to terminate intrauterine pregnancy through 49 days pregnancy. FDA's 2016 REMS changes were in response to Danco's sNDA, which compiled extensive data showing that Mifeprex was safe and effective for use under a *broader* set of conditions. ROA.2159, 2170-2174, 2225-2226. And besides, Plaintiffs filed suit more than six years *after* FDA's 2016 changes.

FDA's 2021 non-enforcement decision likewise did not reopen the narrower 2000 approval. FDA did not substantively reconsider that approval, ROA.4402-4403, alter "the basic regulatory scheme," *NRDC v. EPA*, 571 F.3d 1245, 1266 (D.C. Cir. 2009), or change "the stakes of judicial review" for challenging the 2000 approval, *Sierra Club*, 551 F.3d at 1025 (quotation omitted). The basic regime—Mifeprex is an approved drug subject to certain restrictions—remained unchanged; FDA in 2021 merely announced that it was exercising enforcement discretion as to one specific aspect.

That leaves FDA's 2021 petition denial, in which the District Court's preferred "full review" language appears. ROA.808. But the 2019 citizen petition itself *accepted* FDA's approval of Mifeprex in 2000 with certain use restrictions; it urged FDA to "restore" and "retain" those original restrictions—not to reconsider whether mifepristone should be approved *at all*. *E.g.*, ROA.741-742. The District

Court nevertheless reasoned that by referencing a "full review," FDA must have considered both whether all of the 2016 use restrictions remained necessary *and* whether mifepristone "is too dangerous to be on the market, any mitigation strategy notwithstanding." ROA.4328-4329.

That is wrong. As the stay panel acknowledged, FDA's petition response "did not expressly reconsider its mifepristone approval." ROA.4406. Instead, FDA—like the 2019 petition—treated the 2000 approval "as [a] given." *Ass'n of Am. R.Rs. v. I.C.C.*, 846 F.2d 1465, 1473 (D.C. Cir. 1988). At most, FDA suggested it had considered whether *retaining* all the existing restrictions was necessary to ensure safe and effective use. If the fact that one agency action is "related" to another were "sufficient to restart the … clock" on judicial review, no agency rule would ever be final. *Nat'l Mining Ass'n*, 70 F.3d at 1351; *see Texas v. Biden*, 20 F.4th 928, 953 (5th Cir. 2021), as revised (Dec. 21, 2021) ("incremental adjustments to existing regulations" insufficient) (quotation omitted), *rev'd and remanded*, 142 S. Ct. 2528 (2022).

The stay panel speculated that the 2021 petition denial might potentially trigger constructive reopening because FDA's decision not to enforce the in-person dispensing requirement eliminated "necessary safeguards" from the 2000 approval, ROA.4406 (quoting *Sierra Club*, 551 F.3d at 1025), and "arguably worked" an unanticipated "'sea change' in the legal framework governing mifepristone

distribution that … 'significantly alters the stakes of judicial review,'" ROA.4406 (quoting *Nat'l Biodiesel Bd. v. EPA*, 843 F.3d 1010, 1017 (D.C. Cir. 2016)).

That misunderstands *Sierra Club* and *National Biodiesel Board*. The question there was whether the agency had so altered the regulatory status quo that plaintiffs who lacked adequate notice or incentive to challenge the original decision now had such notice or incentive after the regulatory sea change. In *Sierra Club*, the original rule "may not have been worth challenging"—indeed, the plaintiffs had not challenged it—but the new rule "completely changed" the incentives to seek judicial review and the "stakes" of doing so by fundamentally altering "the regulatory context." 551 F.3d at 1025-26 (quotations omitted). Reopener thus was warranted: EPA's later action "changed the calculus for petitioners in seeking judicial review" of the original decision. *Id.* at 1026. And in *National Biodiesel Board*, the D.C. Circuit *rejected* reopening on the ground that the agency had neither "alter[ed] th[e] regulatory framework nor work[ed]" an unanticipated change. 843 F.3d at 1017. The court therefore declined to excuse plaintiffs' failure to timely challenge the regulatory framework. *Id.*

Compare that to this case. The 2002 citizen petition challenged the 2000 approval, so Plaintiffs clearly believed it was "worth challenging." *Sierra Club*, 551 F.3d at 1026. And the 2021 petition denial did not significantly alter the stakes of seeking judicial review of the 2000 approval: FDA merely confirmed its decision

that time and data had shown some of the original mifepristone restrictions were unnecessary. That was nowhere close to a "sea change," let alone one Plaintiffs could not have "reasonably anticipated," *Nat'l Biodiesel Bd.*, 843 F.3d at 1017 (quotation omitted), "by dint of the statutorily defined [sNDA] process and other similar revision mechanisms," ROA.4407.

Finally, neither the District Court nor the stay panel majority looked, as the reopener doctrine requires, to the "entire context." *Pub. Citizen v. Nuclear Regul. Comm'n*, 901 F.2d 147, 150 (D.C. Cir. 1990). The District Court speculated about what FDA's "full review" might have entailed and whether FDA had considered invoking its statutory authority to withdraw a previously granted approval. *See* ROA.4403-4404;[9] 21 U.S.C. § 355(e). Nothing in the record suggests that option was under consideration.

2. Equitable tolling is inapplicable.

The District Court applied "equitable tolling" to permit Plaintiffs' untimely challenge to the 2000 approval. ROA.4329-4331. The stay panel found this error, for good reason. ROA.4407. Equitable tolling applies "only if the litigant

[9] This analysis was internally inconsistent. The court held the REMS reopened the 2000 approval, ROA.4328, but that FDA's decision to implement a REMS "did not affect … whether an NDA was properly approved or authorized under Subpart H," ROA.4354. Either the REMS reopened and superseded the 2000 approval, rendering any purported Subpart H-based error irrelevant. *See infra* pp. 49-50. Or the REMS did not reopen the 2000 approval, meaning Plaintiffs' challenge to the 2000 approval is time-barred.

establishes two elements: (1) that he has been pursuing his rights diligently, and (2) that some extraordinary circumstances stood in his way and prevented timely filing." *Menominee Indian Tribe of Wis. v. United States*, 577 U.S. 250, 255, 257 (2016). Neither requirement is satisfied.

First, Plaintiffs did not diligently pursue their rights in court or before FDA. They did not "actively pursue [their] judicial remedies," *Irwin v. Dep't of Veterans Affs.*, 498 U.S. 89, 96 (1990), such as by seeking to judicially "compel" FDA to act on their petition, 5 U.S.C. § 706(1). They also did not actively pursue remedies from FDA. The best the District Court could muster was that a member of a Plaintiff-Association *not party* to the 2002 petition twice publicly "called upon" FDA to respond to the petition. ROA.4331 (quoting ROA.234). But equitable tolling does not kick in any time someone publicly urges the Government to take action.

Second, no extraordinary circumstances "beyond [Plaintiffs'] control" prevented their timely filing. *Menominee*, 577 U.S. at 257; ROA.4407. Just the opposite: Plaintiffs had ample opportunity to sue. They failed to do so, even though FDA's delay in adjudicating the 2002 petition *extended their limitations period* all the way through March 2022.

3. Plaintiffs' failure to exhaust is inexcusable.

The stay panel majority suggested Plaintiffs' failure to exhaust their challenge to the 2000 approval in the 2019 petition might be excusable as futile or under an "abuse of process" theory. ROA.4409. Wrong again.

First, the futility "exception is quite restricted," and should be applied "in only the most exceptional circumstances." *Tesoro Refin. & Mktg. Co. v. FERC*, 552 F.3d 868, 874 (D.C. Cir. 2009) (quotations omitted). It "requir[es] a *certainty* of an adverse decision"; that "an unfavorable decision [is] highly likely" does not suffice. *Id.* (cleaned up). On Plaintiffs' own theory, that certainty is lacking here: they (and the District Court) relied on studies and evidence *post-dating FDA's prior decisions* to argue mifepristone is not safe or effective. *See, e.g.*, ROA.94, 144, 482-519, 848-879, 4352-4353. Plaintiffs had no way of knowing how FDA would respond to studies and evidence the agency did not have the opportunity to consider.

Second, the stay panel's novel "abuse of process" theory, which Plaintiffs never invoked, cannot save Plaintiffs' unexhausted claim, as the cases the stay panel cited make clear. ROA.4408-4410. It would not be "a plain miscarriage of justice" to enforce exhaustion here. *Hormel v. Helvering*, 312 U.S. 552, 558 (1941). No intervening decision made the result inevitable. *Cf. id.* at 559-560. Unlike in *Way of Life Television Network, Inc. v. F.C.C.*, 593 F.2d 1356, 1359-60 (D.C. Cir. 1979), the agency did not fault a party for failing to meet an unstated deadline. And

Congress in the APA expressly told Plaintiffs how to handle any perceived "unfairness" or "defect in the administrative process" as a result of FDA's delay in adjudicating their petitions: file a lawsuit seeking to compel agency action unreasonably delayed. *See Washington Ass'n for Television & Child. v. F.C.C.*, 712 F.2d 677, 683 (D.C. Cir. 1983); 5 U.S.C. § 706(1). *Plaintiffs* abused the process by failing to follow that statutorily prescribed path.

C. Plaintiffs' Claims Fail On The Merits.

1. FDA's 2000 approval and subsequent changes were not arbitrary and capricious.

Under the "narrow and highly deferential" APA standard, *Huawei Techs.*, 2 F.4th at 449 (quotation omitted), the questions are whether FDA's actions were "reasonable and reasonably explained," *Prometheus*, 141 S. Ct. at 1158, and whether its factual findings are supported by substantial evidence. *Buffalo Marine Servs.*, 663 F.3d at 753-754. Courts "may not reweigh the evidence, try the issues de novo, or substitute [their] judgment for" the agency's. *Greenspan*, 38 F.3d at 236. FDA's challenged actions easily survive under this standard. FDA acted reasonably in approving Mifeprex in 2000, in adopting the 2016 changes, and in its 2021 non-enforcement decision.

1. The District Court's conclusion that FDA acted arbitrarily turned on an invented "study-match" rule. ROA.4356 n.48. FDA evaluates new drugs by considering whether there is "substantial evidence" of effectiveness from "adequate

and well-controlled investigations" and sufficient evidence of safety, and whether the drug's benefits outweigh any risks. 21 U.S.C. § 355(d). A team of experts (including physicians, statisticians, chemists, pharmacologists, and other scientists) reviews each application and carefully assesses all relevant data in light of the drug's proposed labeling and intended use. If the applicant has demonstrated the drug is safe and effective under the conditions of use in the proposed labeling, and satisfied certain other conditions, FDA *must* approve the drug. 21 U.S.C. §§ 355(c)-(d).

FDA likewise has wide latitude in evaluating proposed REMS modifications. FDA can consider clinical trial data, postapproval studies, adverse event reports and other postmarket safety data, and peer-reviewed scientific literature. *See id.* § 355-1(b)(3). FDA must approve a REMS modification when the modification is necessary to ensure the REMS is not "unduly burdensome on patient access" or to "minimize the burden on the health care delivery system." *Id.* § 355-1(g)(4)(B); *see also id.* § 355-1(f)(2).

These intentionally flexible standards allow FDA to rely on a range of data in evaluating an NDA or REMS and to extrapolate from various sources as it deems appropriate. That flexibility is particularly important because clinical trials often employ more restrictive conditions than those ultimately recommended for approved labeling, a practice intended to protect study participants *before* FDA has concluded

a drug is safe and effective for a particular use. *See* ROA.662; *see also* ROA.3329-3300.

Quite simply, no statutory or regulatory provision prohibits FDA from approving an NDA or REMS where FDA cannot point to one clinical trial evaluating the drug under all of the exact approved conditions of use. FDA can, in its scientific judgment, determine that the existing studies show the drug is safe for use under the proposed labeling. That is what occurred here, and what occurs with virtually every drug on the market. ECF No. 118 at 34-37 (observing that under the District Court's "groundless approach, it is unlikely that a single [drug] would have been approved—or that their approvals would have gone unchallenged—and countless patients would have suffered needlessly").

No agency must have "perfect empirical or statistical data" before it can act; agencies can form a "reasonable predictive judgment" based on the evidence before them. *Prometheus*, 141 S. Ct. at 1160. The District Court erred as a matter of law in finding FDA acted unreasonably in approving the Mifeprex NDA or modifying the REMS without a study that considered the exact proposed combination of conditions. *See id.* at 1161 (Thomas, J., concurring) (lower court erred in "forcing" agency "to consider" an issue statute did not mandate; "[c]ourts have no authority to impose 'judge-made procedur[es]' on agencies) (quoting *Perez v. Mortg. Bankers Ass'n*, 575 U.S. 92, 102 (2015)). This legal error warrants reversal.

2. The District Court also erred in finding FDA acted arbitrarily and capriciously in 2000, 2016, and 2021. Even on the limited record before the lower courts, FDA's approval decisions were reasonable, reasonably explained, and supported by substantial evidence.

Start with 2000. FDA reviewed three clinical trials showing mifepristone was safe and effective—only three women (out of 2,659), for example, required blood transfusions, and the patient's pregnancy was successfully terminated with no further intervention in 92.1-95.5% of cases. ROA.591. FDA carefully evaluated the data and adopted a reasoned set of limited restrictions on Mifeprex's use, while determining other restrictions were not necessary.[10]

Relying on a series of anecdotes and studies post-dating the 2000 approval, none of which were presented to FDA, the District Court concluded FDA nevertheless acted arbitrarily and capriciously. Each decision the District Court second-guessed was well within FDA's expert bailiwick.

The District Court primarily disagreed with FDA's decision to grant providers discretion in the original 2000 approval to determine whether to give a patient an

[10] The District Court appeared to fault FDA for not studying the effects of mifepristone in individuals under 18. Data submitted in the original approval and 2016 changes included testing in under-18 patients. ROA.2188, 2405. FDA waived the pediatric study requirements for premenarchal patients; the requirements for postmenarchal pediatric patients were met. ROA.2149, 2190.

ultrasound. ROA.4357-4360. FDA relied on two clinical trials that established mifepristone was safe and effective when providers were given that discretion. The District Court seemed to fault FDA's reliance on those trials because they were smaller than a U.S. clinical trial. ROA.4355 n.47. But it is up to the agency—not the court—to determine how to weigh clinical trial evidence. *See, e.g.*, *Serono Lab'ys, Inc. v. Shalala*, 158 F.3d 1313, 1327 (D.C. Cir. 1998) ("Neither we, nor the district judge, are scientists independently capable of assessing the validity of the agency's determination—beyond holding it to the standards of rationality required by the [APA]."). And it is flatly impermissible for the court to second-guess the agency's conclusion to grant approval in *2000* based on a smattering of anecdotes and suspect studies post-dating FDA's decision. *See* ROA.4358-4360.

FDA also reasonably concluded special certification programs were unnecessary because "qualified physicians will be using this drug." ROA.595. And FDA adequately ensured any woman who did experience complications would know how to obtain treatment by directing that providers who could not themselves provide surgical intervention give patients contact information for someone who could. *Id.* For women without access to emergency services, the use of Mifeprex was contraindicated.

The District Court also wrongly faulted FDA for acting arbitrarily and capriciously in not evaluating "psychological effects of the drug," ROA.4357, by

which the court appears to mean whether women later regret their choice to have an abortion. This, again, criticizes FDA for something that it is not directed to do by 21 U.S.C. § 355(d). It also relies, again, on sources post-dating mifepristone's approval by decades. And those sources are not even specific to medication abortion—they discuss *all types* of pregnancy loss. ROA.4357 (citing ROA.3495).

Nor was it arbitrary and capricious for FDA to approve Mifeprex after raising—and resolving—concerns over the course of its review of the NDA. *See, e.g.*, ROA.4360-4363. Were FDA never permitted to approve a drug after engaging in discussions about its safety and efficacy, most drugs would never be approvable. As FDA recognized, "[i]t is not unusual for such differences to emerge during the course of the review process for a proposed drug product." ROA.651. After evaluating significant evidence, FDA found Mifeprex safe and effective under the conditions of use and reasonably explained its decision. Its determination was not arbitrary and capricious.

Plaintiffs' challenge to FDA's 2016 changes fares no better. In 2016, FDA looked at dozens of studies covering tens of thousands of women, including studies that specifically addressed every single change FDA was considering:

- 20 studies including over 35,000 women supporting the conclusion that the new dosing regimen would be safe and effective, ROA.2170-2174, 2202-2203;

- seven studies including 934 women supporting increasing the gestational-age cutoff, ROA.2179-2180, 2203;
- 11 studies including 30,763 women supporting home administration of misoprostol, ROA.2182-2183, and showing "adverse events equal to or lower than those with the approved regimen requiring in-office dispensing of misoprostol," ROA.2204;
- four studies including 3,200 women supporting non-physician prescribing of Mifeprex, ROA.2185-2186;[11]
- one study involving over 45,000 women supporting increased flexibility for follow-up appointments, ROA.2186;
- *and* 15 years of data showing Mifeprex's safe use under various conditions, ROA.2201-2202.

The District Court suggested that FDA's decision to remove safeguards has harmed women. ROA.4358-4360. The data overwhelmingly disproves the court's scattershot examples. At the time of the 2016 changes, fewer than 0.13% of the over 2.5 million U.S. women who had used Mifeprex had experienced any adverse event,

[11] Consistent with FDA's deference to state regulation of the practice of medicine, including whether advanced practice providers can prescribe drugs, all approved REMS programs universally refer to "prescribers" and "healthcare providers," rather than physicians. *See* FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS)*, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (last visited Apr. 26, 2023) (FDA, *REMS*).

as reflected in the mandatory provider adverse-event reporting. ROA.2225-2226. Despite those low numbers from mandatory reporting, the District Court suggested that FDA "shirked" its responsibilities by ending heightened mandatory provider reporting of serious adverse events in 2016. ROA.4365. But even after the 2016 changes, mifepristone remains subject to a *more rigorous adverse event reporting regime* than the vast majority of drugs. The mifepristone REMS is one of only five REMS programs for which FDA requires prescribers to report deaths of *any* cause in patients who receive the drug. *See* FDA, *REMS*, *supra* note 11. On top of that, Danco is bound by 21 C.F.R. § 314.80 and § 314.81 to report serious, unexpected adverse events to FDA within 15 days, and all others on an annual basis. Providers like Plaintiff-physicians and the Plaintiff-Association members also can voluntarily report adverse events directly to FDA, including through an online form. *See* 21 C.F.R. § 20.112; FDA, *Medwatch Online Voluntary Reporting Form*, https://www.accessdata.fda.gov/scripts/medwatch/ (last visited Apr. 26, 2023).

The 2021 non-enforcement decision was likewise supported by ample evidence. FDA examined actual postmarketing safety data from an eight-month period during which in-person dispensing was not enforced due to the COVID-19 pandemic. ROA.827-829. That data showed "no indication" that relaxing the in-person dispensing requirement "contributed to … adverse events." ROA.827-828. Based on this, FDA concluded "that mifepristone may be safely used without in-

person dispensing." ROA.829. FDA also examined three studies permitting mail-order pharmacy dispensing and five studies allowing clinic dispensing by mail, all of which supported the conclusion that mifepristone would still be safe and effective even with a relaxed in-person dispensing requirement. ROA.833-836.

The District Court did not conclude otherwise; it enjoined FDA's 2021 changes entirely on its interpretation of the Comstock Act. ROA.4344-4345. More on that shortly; *see infra* pp. 52-56. The stay panel, for its part, concluded Plaintiffs were likely to succeed in showing the 2021 changes were arbitrary and capricious based solely on the elimination of the adverse reporting requirement. ROA.4412. That fails for the reasons explained.

In short, FDA relied on abundant data; exercised its scientific expertise; made "a reasonable predictive judgment based on the evidence it had"; and "reasonably explained" its decision approving Mifeprex in 2000, and in promulgating the 2016 and 2021 changes. *Prometheus*, 141 S. Ct. at 1160. Courts may not second-guess that scientific decision making, particularly when it comes to consequential matters of public health. *See id.* at 1159-60. In fact, this is the first time a court has ever second-guessed FDA's scientific judgment by enjoining a drug's approval on the ground that FDA got the science wrong.

2. FDA's initial reliance on Subpart H has no legal effect today, and was permissible in any event.

Mifepristone is subject today to FDA's REMS authority. "Deemed" by Congress in 2008 to have a REMS in place, Mifeprex's REMS was formally approved by FDA in 2011. *Supra* pp. 5-6. The District Court's view that FDA should not have used Subpart H to impose use restrictions from 2000-2008 is an entirely academic question.

Before the 2008 enactment of the REMS authority in 21 U.S.C. § 355-1, FDA relied on its authority under 21 U.S.C. § 355 to approve Mifeprex, and its authority under Subpart H to impose "restrictions to assure safe use" prior to approving a drug otherwise "shown to be effective." *See* 21 C.F.R. § 314.520. In the 15 years since Congress enacted § 355-1, FDA has never relied on Subpart H to impose use restrictions; it uses the REMS authority in § 355-1.

FDA's approval of the mifepristone REMS formalized Mifeprex's conversion from having certain restrictions under Subpart H to having restrictions under a REMS. Simply put, Subpart H plays *no role* in the use restrictions applicable to mifepristone today.

The District Court misunderstood the statutory and regulatory scheme. It erroneously suggested that FDA had "accelerated" the Mifeprex approval. ROA.4346-4347, 4350. Incorrect. Separate Subpart H provisions cover accelerated

approval and use restrictions. *Compare* 21 C.F.R. § 314.510 *with* 21 C.F.R. § 314.520(a); *supra* note 2. FDA used only the latter back in 2000.[12]

The District Court also misunderstood the effect of the REMS framework. It thought Congress's decision to "deem" mifepristone to have a REMS was merely designed to "ease[] the regulatory transition from Subpart H to the REMS provision." ROA.4354. In fact, by "deem[ing]" drugs approved prior to 2007 "to have in effect an approved [REMS]," Congress effectively superseded FDA's prior decision to implement use restrictions under Subpart H. Pub. L. No. 110-85, § 909(b)(1). FDA's later approval of Danco's REMS submission in 2011 completed the transition to REMS-governed use restrictions under § 355-1. There is no legal justification for effectively vacating mifepristone's approval *today* based on Subpart H's pre-2008 role in the drug's *initial* use restrictions. *See Allied-Signal, Inc. v. U.S. Nuclear Regul. Comm'n*, 988 F.2d 146, 150-151 (D.C. Cir. 1993) (discussing standard for remand without vacatur); *infra* p. 61.

Regardless, FDA properly invoked its Subpart H authority to implement use restrictions when it approved Mifeprex. Subpart H "applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to

[12] Mifeprex's approval was far from fast. It took FDA 54 months to approve the drug—more than three times the then-average duration for a drug approval. 2008 GAO Report, *supra*, at 27.

patients over existing treatments." 21 C.F.R. § 314.500. Consistent with FDA's interchangeable use of "illness," "condition," and "disease" under the FDCA, the agency reasonably concluded that it could use Subpart H to approve drugs to treat a variety of conditions that some may not consider an "illness"—including Mifeprex. *See* New Drug, Antibiotic, and Biological Drug Product Regulations, 57 Fed. Reg. 58,942, 58,946 (Dec. 11, 1992). Mifeprex is not an outlier in that respect: FDA likewise used Subpart H to approve drugs for acute acne, infertility, and inflammation. *See* 2008 GAO Report, *supra*, at 4-5; ECF No. 112 at 18-19. To the extent doubt remains, FDA's construction deserves deference under *Kisor v. Wilkie*, 139 S. Ct. 2400, 2415-18 (2019).

FDA also reasonably exercised its scientific expertise to determine that Mifeprex has a "meaningful therapeutic benefit" over surgical abortion. *Infra* pp. 57-59. The APA does not imbue a reviewing court with license to replace the agency's expert judgment with its own view. That is especially true when the court relied on its independent research and on sources post-dating the agency's various approvals—including a study of a small number of anonymous blog posts on a website called AbortionChangesYou.com. *See* ROA.507-519.[13] APA review must be "limited to the record before the agency at the time of its decision." *Fort Bend*

[13] *See generally* Unikowsky, *supra* note 8 (discussing same).

County v. U.S. Army Corps of Eng'rs, 59 F.4th 180, 196 (5th Cir. 2023) (quotation omitted).

D. Plaintiffs' Comstock Act Argument Fails.

1. The District Court concluded FDA likely violated the Comstock Act in 2021 when it exercised enforcement discretion and permitted mifepristone to be distributed to patients by mail. But the court should never have reached that admittedly unexhausted issue. *See* ROA.4215-4216. The court's attempts to excuse Plaintiffs' failure to exhaust are wrong at every turn.

First, the District Court found judicial review appropriate because the 2021 non-enforcement decision is "contrary to [the Comstock Act's] important public policy." ROA.4334 (quotation omitted). Its only support for this purported exception is *Myron v. Martin*, a 41-year-old Fifth Circuit decision that *declined* to excuse a failure to exhaust. 670 F.2d 49, 52 (5th Cir. 1982). If courts can excuse failure to exhaust because the subject statute embodies "important public policy," Katy bar the door.

Second, the court found that requiring Plaintiffs to exhaust their Comstock Act claim would "result in individual injustice or cause irreparable injury," again exclusively citing cases that refused to excuse exhaustion. ROA.4335 (quotations omitted). Someone go help Katy. Besides, the court is wrong on the equities. *Infra* pp. 56-62.

Third, relying on *Coit Indep. Joint Venture v. Fed. Sav. & Loan Ins. Corp.*, 489 U.S. 561, 587 (1989), the District Court opined that Plaintiffs need not present this claim to FDA because the agency's prior delays "shows [its] procedures have been inadequate." ROA.4336. In *Coit*, there was no "time limit" on agency action—meaning the agency could delay administrative processing indefinitely *while* the limitations-clock was ticking. 489 U.S. at 586-587. Here, there is a time limit and a judicially-enforceable remedy if FDA misses that deadline. *See* 21 C.F.R. § 10.30(e); 5 U.S.C. § 706(1). *Plaintiffs*' choice not to exercise those options does not render *FDA*'s procedures inadequate.

Fourth, the District Court found exhaustion futile, even though Plaintiffs never presented this claim to FDA. ROA.4336-4337. The failure to exhaust is not excusable where plaintiffs decline to raise an argument on speculation that "the agency *would reject it* in the *future*." *Tesoro*, 552 F.3d at 874. And the agency statements the court invoked to find futility issued *after* Plaintiffs filed suit. *See* ROA.4336-4337. An agency's expected or stated adverse litigation position does not render exhaustion "futile."

Finally, the court held that Plaintiffs had raised their Comstock Act claim with "sufficient clarity" because (1) the 2019 petition mentioned keeping in-person dispensing (but not Comstock); and (2) the Postal Service and Department of Health and Human Services asked the Office of Legal Counsel (OLC) for an opinion

concerning Comstock after FDA issued the 2021 changes, and OLC mentioned "FDA's [medication abortion] regimen" in response. ROA.4337. None of that answers whether Plaintiffs raised the issue "with sufficient clarity *to allow the decision maker to understand and rule on the issue raised*." ROA.4334 (emphasis added and quotation omitted). The answer is no. Nobody ever raised the Comstock Act to "the decision maker"—*FDA*.

Regardless, any claim based on the 2021 non-enforcement statement was mooted when FDA permanently removed the in-person dispensing requirement. *See* Ctr. for Drug Evaluation & Rsch., *Approval Package for NDA 20-687/S-025* (Jan. 3, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/020687Orig1s025.pdf. Plaintiffs did not amend their complaint or raise a challenge to the 2023 REMS at any point in the briefing or at the hearing. *See* ROA.3240-3252, 4195-4227. The court lacked jurisdiction to issue a preliminary injunction based on a superseded exercise of enforcement discretion.

2. The District Court's Comstock Act analysis also fails on the merits. The premise of the court's order is that FDA was obligated to evaluate the Comstock Act in considering mifepristone's approval conditions. The assumption is misplaced for multiple reasons.

One: Neither Plaintiffs nor the District Court pointed to a single case requiring agencies to scour the capacious U.S. Code to identify every statute that

might potentially apply to some aspect of agency operations. In the face of that silence, it is unsurprising that FDA did not address an 1873 criminal statute that it is not charged with interpreting or enforcing (or the myriad other laws that might govern approved drugs, like state tort laws or laws directed to the SEC or IRS).

Two: FDA is not *allowed* to orient NDAs or REMS around a criminal statute beyond FDA's purview. *See DeNaples v. Off. of Comptroller of Currency*, 706 F.3d 481, 490 (D.C. Cir. 2013). By statute, FDA may consider only seven grounds in approving or denying an NDA. 21 U.S.C. § 355(d). If none applies, FDA "shall issue an order approving the application." *Id.* Compliance with criminal laws—or any other laws that FDA is not tasked with administering—is not on that list.

Three: When FDA took the challenged actions, *Roe v. Wade* was governing law—so the Comstock Act could not have been constitutionally enforced to prohibit the mailing of mifepristone. Under the APA, the lawfulness of agency action must be evaluated by looking to the law at the time the agency acted. *See Circus Circus Casinos, Inc. v. NLRB*, 961 F.3d 469, 476 (D.C. Cir. 2020). The District Court theorized that FDA should nevertheless have considered whether enforcing the Comstock Act might not run afoul of *Casey*'s undue burden test. ROA.4344. That still does not explain why FDA was *affirmatively* required to find and discuss this criminal law. Nor does it explain how FDA, an agency charged with "promot[ing] the public health by … reviewing clinical research" and acting "on the marketing of

regulated products," would have the authority to interpret that criminal law. *See* 21 U.S.C. § 393(b)(1); *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 161 (2000) (agencies may not regulate absent valid congressional grant of authority).

Finally, multiple courts of appeals and OLC have interpreted the statute to restrict only the sending of items intended for *unlawful* abortions. *See* ROA.2343-2349 (collecting cases). FDA was not required to diverge from these considered views, especially where the rule of lenity favors the narrower construction. *See, e.g.*, *Leocal v. Ashcroft*, 543 U.S. 1, 11 n.8 (2004) (lenity applies in civil context where criminal statute has "both criminal and noncriminal applications").

II. THE EQUITIES OVERWHELMINGLY FAVOR DEFENDANTS.

The District Court's equities analysis is as mistaken as its merits analysis. It claimed to be maintaining the status quo by merely "stay[ing]" an approval that went into effect 23 years ago. ROA.4373. But the ruling is plainly a "particularly disfavored" mandatory injunction that upends a decades-long status quo. *Martinez*, 544 F.2d at 1243. And the equities overwhelmingly favor denying injunctive relief, mandatory or otherwise.

A. Danco Faces Substantial, Certain, Unrecoverable Harm.

The District Court's ruling effectively made marketing and distributing mifepristone unlawful under the FDCA while this case proceeds. Mifeprex is Danco's only product, and under the ruling below, Danco would likely be unable to

continue operations. ECF No. 29 at 78, ¶ 11. The District Court completely ignored this undeniably irreparable harm to Danco. *See Atwood Turnkey Drilling, Inc. v. Petroleo Brasileiro, S.A.*, 875 F.2d 1174, 1179 (5th Cir. 1989) ("potential economic loss" that "threaten[s] the existence of the movant's business" is irreparable). That was error. *See Direct Biologics L.L.C. v. McQueen*, 63 F.4th 1015, 1020 (5th Cir. 2023) (court must "consider the effect on each party") (quotation marks omitted).

The harm to Danco cannot be ameliorated by enjoining only the 2016 or 2021 FDA actions. FDA has made clear that such an order will render misbranded all extant doses of Mifeprex. Woodcock Decl. ¶¶ 15-16.[14] Distributing a misbranded product will expose Danco to severe civil or criminal penalties. *See* Woodcock Decl. ¶ 15; 21 U.S.C. § 331(a). The company would therefore be unable to distribute its sole product for the months it would take to prepare a new sNDA; for FDA to review and approve the sNDA; and for Danco to relabel Mifeprex, implement the modified REMS, including re-certifying prescribers with new provider agreement forms, and update its distribution model. *See* Woodcock Decl. ¶¶ 14-15; Long Decl. ¶¶ 11-12, 26.[15] This will irreparably harm the one-product pharmaceutical company.

[14] The Woodcock declaration is available in the appendix to the stay application filed in Supreme Court No. 22A902, beginning on page 110a.
[15] The Long declaration is available in the appendix to the stay application filed in Supreme Court No. 22A901, beginning on page 110a.

B. The Public Interest Favors The Government And Danco.

The public interest favors continued access to a safe and effective drug that is approved for use in 94 countries worldwide;[16] has been on the World Health Organization's Model List of Essential Medicines for more than 15 years;[17] and has been relied on by over 5 million women in this country as the standard of care for medication abortions for more than two decades.

The District Court's contrary analysis rests on a false narrative that does not account for the interests of the more than 96% of women for whom mifepristone is effective, ROA.2170-2174, and the more than 99.9% of women who do not experience any serious adverse event, ROA.2189, 2198, 2224-2227. As numerous amicus briefs and declarations have emphasized, under the District Court's injunction, many women unable to obtain a mifepristone prescription would be forced to undergo more complicated, more intrusive, riskier, and later-gestational age surgical abortions; turn to unapproved regimens with a lower complete success rate and more intense side effects; obtain drugs from abroad; or to continue a non-viable or unwanted pregnancy—and endure the risks, complications, and psychological harms attendant to these alternatives. *E.g.*, ECF No. 29 at 71-73,

[16] *See* Gynuity Health Projects, *Mifepristone Approved List* (updated Mar. 2023), https://gynuity.org/assets/resources/mapmifelist_en.pdf.
[17] *See* World Health Org., *WHO Model List of Essential Medicines – 22nd List, 2021* (Sept. 30, 2021), https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02.

¶¶ 10-11, 13-14; *id.* at 84, 86-89, ¶¶ 12, 18-22; ECF No. 111 at 27-29; ECF No. 63 at 23-30. The court's order also harms the doctor-patient relationship by prohibiting doctors from recommending medication abortion when, in their medical judgment, it is the best course of treatment for a particular patient's circumstances. *See* ECF No. 29 at 73, ¶ 15; *id.* at 87-88, ¶¶ 19, 21.

As the American College of Obstetricians and Gynecologists explained, enjoining any of FDA's challenged actions also creates serious health risks and denies access to essential medical care for patients who use mifepristone off-label for miscarriage management, to reduce the duration of bleeding during certain serious pregnancy complications, and for maternal health purposes. ROA.3584-3585; *see also, e.g.*, S. File No. 0109, § 1(b)(ii), 67th Leg., 2023 Gen. Sess. (Wyo. 2023).

The decision below destabilizes the pharmaceutical industry. As *over 700* pharmaceutical executives emphasized in supporting FDA's regulatory authority, the court's rogue decision diminishes FDA's authority over drug approvals, creates uncertainty for the industry, reduces incentives for investment, and puts any medicine at risk for the same outcome. *See* Carma Hassan, *Drugmakers Sign Letter Supporting FDA and Calling for Reversal of Texas Judge's Mifepristone Ruling*, CNN.com (Apr. 10, 2023), https://www.cnn.com/2023/04/10/health/mifepristone-drugmakers-letter/index.html (linking to letter); *see also* ECF No. 118

(pharmaceutical company, executives, and investors amicus brief detailing industry harms); PhRMA Amicus Br. at 18-21[18] (same from Pharmaceutical Research and Manufacturers of America).

Until this case, no court had ever ordered a drug to be pulled from the market based on its reassessment of FDA's safety and efficacy determination. The role of Article III courts is to say what the law is, not to say what a judge might have done if he were FDA Commissioner. The public interest is served by respecting the particular capability of this expert agency—and all of its physicians, data scientists, statisticians, chemists, pharmacologists, and other scientists—to decide questions of drug safety.

Vacating the injunction would also serve the interests of all 50 states and preserve the separation of powers. Under *Dobbs v. Jackson Women's Health Org.*, "the people and their elected representatives" enjoy the power to regulate abortion. 142 S. Ct. 2228, 2259 (2022). The injunction eviscerates that sovereign authority for States that wish "to protect the right to choose to terminate a pregnancy," ROA.2889; imposes "heightened health and economic costs" on local governments, ECF No. 125 at 17-18; burdens overwhelmed public hospital systems, *see* ECF No. 117 at 33-36; and upsets Congress's decision to assign FDA responsibility for safety

[18] *Available at* Supreme Court Docket No. 22A902.

and efficacy determinations, which courts review for substantial evidence and with significant deference, *see* ECF No. 110 at 29-33.

Any half-measure that leaves the 2000 approval in place and enjoins only later FDA action(s) will exacerbate these harms, not alleviate them. Requiring a return to a prior and outdated REMS and label would also create months-long loss of access, while FDA and Danco work through the sNDA process. *See* Woodcock Decl. ¶ 14; *supra* p. 57.

Even if Plaintiffs win on the merits, moreover, the appropriate remedy would be remand without vacatur to allow FDA to consider and remedy any issue the Court identifies. *Cent. & S. W. Servs. v. EPA*, 220 F.3d 683, 692 (5th Cir. 2000). That is especially so given "the disruptive consequences" that may otherwise result. *Allied-Signal*, 988 F.2d at 150-151 (quotation omitted). A preliminary injunction cannot award a party more relief than would be available on the merits, *De Beers Consol. Mines v. United States*, 325 U.S. 212, 220 (1945)—but that is effectively what the District Court did, causing significant disruption and harm to the public interest.

C. Plaintiffs Face No Irreparable Harm Absent An Injunction.

Plaintiffs claim irreparable injury from speculative concerns about having to provide follow-up surgical abortion care in emergency rooms in response to discretionary actions by third parties who want to prescribe and be prescribed mifepristone—an eventuality that will rarely, if ever, occur given (1) the tiny number

of women who have historically sought such care in emergency rooms and (2) conscience-clause protections for doctors who do not wish to provide such care.

Plaintiffs' dilatory actions further undermine any speculative claims of irreparable injury. *See Holmberg v. Armbrecht*, 327 U.S. 392, 396 (1946) ("equitable relief" inappropriate when plaintiff "inexcusably slept on his rights"). Plaintiffs waited over six years after FDA denied their 2002 citizen petition, and nearly a year after FDA denied their 2019 citizen petition, to file suit. They chose not to seek to compel FDA to act sooner, *see* 5 U.S.C. § 706(1), or to otherwise negotiate with FDA in the interim, *cf. Optimus Steel, L.L.C. v. U.S. Army Corps of Eng'rs*, 492 F. Supp. 3d 701, 720 (E.D. Tex. 2020). Nor did they seek a temporary restraining order. Most tellingly, Plaintiffs proposed a schedule that would have delayed any ruling by several months, to allow the District Court to obtain the full administrative record and issue a decision on the merits. ROA.3240-3252. Plaintiffs cannot now claim that they will suffer irreparable injury if a drug that has been on the market for nearly 23 years remains on the market while the District Court does exactly that.

CONCLUSION

For the foregoing reasons, the Court should vacate the District Court's decision.

Respectfully submitted,

/s/ Jessica L. Ellsworth
JESSICA L. ELLSWORTH
CATHERINE E. STETSON
KAITLYN A. GOLDEN
DANIELLE DESAULNIERS STEMPEL
MARLAN GOLDEN
DELIA SCOVILLE
HOGAN LOVELLS US LLP
555 Thirteenth Street, N.W.
Washington, D.C. 20004
(202) 637-5600
jessica.ellsworth@hoganlovells.com

PHILIP KATZ
LYNN W. MEHLER
HOGAN LOVELLS US LLP
555 Thirteenth Street, N.W.
Washington, D.C. 20004

EVA M. SCHIFINI
HOGAN LOVELLS US LLP
1999 Avenue of the Stars
Suite 1400
Los Angeles, CA 90067

Counsel for Intervenor-Appellant

CERTIFICATE OF SERVICE

I hereby certify that, on April 26, 2023, I electronically filed the foregoing with the Clerk of Court by using the appellate CM/ECF system. I further certify that the participants in the case are CM/ECF users and that service will be accomplished by using the appellate CM/ECF system.

/s/ Jessica L. Ellsworth
Jessica L. Ellsworth

Counsel for Intervenor-Appellant

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B), because it contains 12,985 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the typestyle requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Word for Office 365 in Times New Roman 14-point font.

/s/ Jessica L. Ellsworth
Jessica L. Ellsworth

Counsel for Intervenor-Appellant

ADDENDUM

TABLE OF CONTENTS

Page

21 U.S.C. § 355(c)(1)(A) ..... Add. 1

21 U.S.C. § 355(d) ..... Add. 2

21 U.S.C. § 355(e) ..... Add. 4

21 U.S.C. § 355-1(a)(1) ..... Add. 6

21 U.S.C. § 355-1(f)(2) ..... Add. 7

21 U.S.C. § 355-1(g)(4) ..... Add. 8

Food and Drug Admin. Amends. Act of 2007: Pub. L. No. 110-85, tit. IX, § 909(b)(1) ..... Add. 9

Food and Drug Admin. Amends. Act of 2007: Pub. L. No. 110-85, tit. IX, § 909(b)(3) ..... Add. 10

21 U.S.C. § 355

§ 355. New drugs

* * *

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b), or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) approve the application if he then finds that none of the grounds for denying approval specified in subjection (d) applies, or

* * *

21 U.S.C. § 355

§ 355. New drugs

* * *

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b); or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the

Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marking approval of a drug.

* * *

21 U.S.C. § 355

§ 355. New drugs

* * *

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) or to comply with the notice requirements of section

360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based. The Secretary may withdraw the approval of an application submitted under this section, or suspend the approval of such an application, as provided under this subsection, without first ordering the applicant to submit an assessment of the approved risk evaluation and mitigation strategy for the drug under section 355-1(g)(2)(D) of this title.

* * *

21 U.S.C. § 355-1

§ 355-1. Risk evaluation and mitigation strategies

* * *

(a) Submission of proposed strategy

(1) Initial Approval

If the Secretary, in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety with respect to the drug, determines that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug, and informs the person who submits such application of such determination, then such person shall submit to the Secretary as part of such application a proposed risk evaluation and mitigation strategy. In making such a determination, the Secretary shall consider the following factors:

(A) The estimated size of the population likely to use the drug involved.

(B) The seriousness of the disease or condition that is to be treated with the drug.

(C) The expected benefit of the drug with respect to such disease or condition.

(D) The expected or actual duration of treatment with the drug.

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

(F) Whether the drug is a new molecular entity.

* * *

21 U.S.C. § 355-1

§ 355-1. Risk evaluation and mitigation strategies

* * *

(f) Providing safe access for patients to drugs with known serious risks that would otherwise be unavailable

(2) Assuring access and minimizing burden

Such elements to assure safe use under paragraph (1) shall—

(A) be commensurate with the specific serious risk listed in the labeling of the drug;

(B) within 30 days of the date on which any element under paragraph (1) is imposed, be posted publicly by the Secretary with an explanation of how such elements will mitigate the observed safety risk;

(C) considering such risk, not be unduly burdensome on patient access to the drug, considering in particular—

(i) patients with serious or life-threatening diseases or conditions;

(ii) patients who have difficulty accessing health care (such as patients in rural or medically underserved areas); and

(iii) patients with functional limitations; and

(D) to the extent practicable, so as to minimize the burden on the health care delivery system—

(i) conform with elements to assure safe use for other drugs with similar, serious risks; and

(ii) be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

* * *

21 U.S.C. § 355-1

§ 355-1. Risk evaluation and mitigation strategies

* * *

(g) Assessment and modification of approved strategy

(4) Modification

(A) On initiative of responsible person

After the approval of a risk evaluation and mitigation strategy by the Secretary, the responsible person may, at any time, submit to the Secretary a proposal to modify the approved strategy. Such proposal may propose the addition, modification, or removal of any goal or element of the approved strategy and shall include an adequate rationale to support such proposed addition, modification, or removal of any goal or element of the strategy.

(B) On initiative of Secretary

After the approval of a risk evaluation and mitigation strategy by the Secretary, the Secretary may, at any time, require a responsible person to submit a proposed modification to the strategy within 120 days or within such reasonable time as the Secretary specifies, if the Secretary, in consultation with the offices described in subsection (c)(2), determines that 1 or more goals or elements should be added, modified, or removed from the approved strategy to—

(i) ensure the benefits of the drug outweigh the risks of the drug;

(ii) minimize the burden on the health care delivery system of complying with the strategy; or

(iii) accommodate different, comparable aspects of the elements to assure safe use for a drug that is the subject of an application under section 355(j) of this title, and the applicable listed drug.

* * *

Food and Drug Admin. Amends. Act of 2007: Pub. L. No. 110-85, tit. IX

§ 909. EFFECTIVE DATE AND APPLICABILITY.

* * *

(b) DRUGS DEEMED TO HAVE RISK EVALUATION AND MITIGATION STRATEGIES.—

(1) IN GENERAL.—A drug that was approved before the effective date of this Act is, in accord`ance with paragraph (2), deemed to have in effect an approved risk evaluation and mitigation strategy under section 505–1 of the Federal Food, Drug, and Cosmetic Act (as added by section 901) (referred to in this section as the "Act") if there are in effect on the effective date of this Act elements to assure safe use—

(A) required under section 314.520 or section 601.42 of title 21, Code of Federal Regulations; or

(B) otherwise agreed to by the applicant and the Secretary for such drug.

* * *

Food and Drug Admin. Amends. Act of 2007: Pub. L. No. 110-85, tit. IX

§ 909. EFFECTIVE DATE AND APPLICABILITY.

* * *

(b) DRUGS DEEMED TO HAVE RISK EVALUATION AND MITIGATION STRATEGIES.—

(3) SUBMISSION.—Not later than 180 days after the effective date of this Act, the holder of an approved application for which a risk evaluation and mitigation strategy is deemed to be in effect under paragraph (1) shall submit to the Secretary a proposed risk evaluation and mitigation strategy. Such proposed strategy is subject to section 505–1 of the Act as if included in such application at the time of submission of the application to the Secretary.

* * *