Nos. 23-235, 23-236

In the Supreme Court of the United States

FOOD AND DRUG ADMINISTRATION ET AL.,

PETITIONERS,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.

DANCO LABORATORIES, L.L.C., PETITIONER,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.

ON WRITS OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

BRIEF FOR *AMICUS CURIAE* GENBIOPRO, INC. SUPPORTING PETITIONERS

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STATEMENT OF INTEREST[1]

GenBioPro, Inc. has held a U.S. Food and Drug Administration ("FDA")-approved Abbreviated New Drug Application ("ANDA") to market generic mifepristone since 2019. GenBioPro is the sole supplier of generic mifepristone in the United States, and its mifepristone business constitutes approximately 95% of its revenue. Any significant change to the requirements or conditions of FDA's approval of mifepristone will have substantial negative effects on GenBioPro's business.

Mifepristone is subject to a special set of FDA conditions known as a Risk Evaluation and Mitigation Strategy ("REMS"), which Congress has directed must be designed in a way that "assur[es] access and minimize[s] burden" on "the health care delivery system." 21 U.S.C. § 355-1(f)(2), (f)(2)(D). The Fifth Circuit's judgment in this case affirmed the district court's preliminary order purporting to "stay" certain modifications to the REMS and to other conditions of use for mifepristone that FDA approved in 2016—three years before FDA approved GenBioPro's ANDA and GenBioPro began selling the drug. The decision thus compels FDA to turn back the clock to an obsolete regulatory regime under which GenBioPro has never before operated. Unlike a traditional "stay" of administrative action—which preserves the status quo—the lower courts' decisions here impose retroactive changes to the regulatory regime for products that have been lawfully sold for years, and potentially for products already in the stream of commerce. And because the decision below is preliminary in nature, efforts to comply with the radically altered

[1] No counsel for a party authored this brief in whole or in part. No person other than GenBioPro, its members, or its counsel made a monetary contribution to its preparation or submission.

regulatory scheme would all be wasted if the final judgment differs from the provisional remedy.

The Fifth Circuit's decision purporting to modify mifepristone's conditions of use threatens enormous harm to GenBioPro, its customers, and patients nationwide. If the Fifth Circuit's decision stands and goes into effect, GenBioPro may be unable to sell mifepristone because adapting to the pre-2016 conditions would require GenBioPro to make significant changes to its product and marketing practices. Even though Respondents' claim directly challenging GenBioPro's ANDA approval is not before this Court because the Fifth Circuit rejected it, its labeling must nonetheless match the label of brand-name Mifeprex. Accordingly, GenBioPro would need to wait to seek approval of those changes until the brand-name manufacturer, Petitioner Danco Laboratories, L.L.C., receives approval for its own labeling change. And even after GenBioPro's product is reapproved, the market to which it regains access would not resemble any status quo ante; under the pre-2016 conditions the Fifth Circuit imposed, telemedicine providers and mail-order pharmacies constituting a substantial proportion of GenBioPro's customer base will no longer be able to prescribe or dispense GenBioPro's product. GenBioPro accordingly has a concrete and pressing interest in avoiding the harm to itself, its partners, its customers, and the patients it serves that would result if the Fifth Circuit's decision takes effect.

INTRODUCTION AND SUMMARY OF ARGUMENT

Last April, this Court stayed an unprecedented district court order that admittedly "second-guess[ed] FDA's decisionmaking" as to the safety and regulation of mifepristone, Pet. App. 182a, a drug that has been used safely and effectively by millions of Americans for more

than two decades.[2] The Fifth Circuit's decision now under review engages in further judicial second-guessing, affirming the district court's purported "stay" of FDA's scientific judgment—based on years of experience and analysis of clinical research and other safety data—about whether certain conditions of use and restrictions on mifepristone were necessary for its safe use. Pet. App. 4a.

The Fifth Circuit's second-guessing of FDA safety decisions violated fundamental principles of judicial review under the Administrative Procedure Act ("APA"). The court refused to accord the deference that this Court has long demanded whenever courts review challenges to scientific determinations by FDA and other agencies. And the Fifth Circuit did so without FDA having had an opportunity to produce the administrative record containing the scientific evidence on which it relied, and paying no deference at all to FDA's careful consideration of that record.

Not long ago, this Court stayed another district court's order, holding that it had improperly interfered with FDA's decisionmaking on one of the same restrictions for mifepristone at issue in this case. *FDA* v. *Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 10, 11 (2020); *FDA* v. *Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578, 578 (2021). Without even acknowledging those rulings, the Fifth Circuit overrode FDA decisionmaking on the *same issue*, disrupting the status quo, and doing so based on a deeply flawed analysis of an incomplete record.

This Court has warned against judicial interference with FDA's reasoned scientific determinations. The Fifth

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[2] In citing the rulings below, this brief references FDA's Petition Appendix in No. 23-235. For other record citations, this brief refers to FDA's Joint Appendix ("J.A.") filed in this Court and the Record on Appeal ("ROA") filed in the Fifth Circuit.

Circuit's decision demonstrates the wisdom of that policy of restraint—particularly on an incomplete record. For instance, the Fifth Circuit below did not question FDA's determination that every individual aspect of its 2016 modifications to mifepristone's use conditions ensured that mifepristone remained a safe and effective drug. Yet without citing any evidence or record support—or any legal authority other than the motions panel that initially reviewed the district court's "stay" order last spring—the Fifth Circuit speculated that the "cumulative" effect of the 2016 modifications *could* be unsafe, calling that an "important aspect of the problem." Pet. App. 54a.

In fact, the court never examined the clinical studies underlying and amply supporting FDA's 2016 changes, which reported that thousands of patients had successfully and safely used mifepristone under the modified conditions. Without the administrative record, it is unclear how the Fifth Circuit could have confirmed that FDA "failed to consider" an "aspect of the problem." Pet. App. 74a. Instead, violating black-letter principles of APA review, the Fifth Circuit simply "substitute[d] its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). The court compounded its errors by failing to consider the extensive evidence that FDA's actions reasonably implemented Congress's mandate to balance safety *and access* in adopting and revising a REMS. See 21 U.S.C. § 355-1(f).

The real-world consequences of the Fifth Circuit's erroneous ruling are severe. The court itself recognized that its holding would cause "significant injury" to Danco to the extent it may be prohibited from selling any of its existing product until it obtains FDA approval for revised labeling. Pet. App. 66a. And GenBioPro will endure those harms to an even greater degree. Because the labeling for

its generic mifepristone must match Danco's precisely, GenBioPro is at risk of being required to wait for Danco's reapproval before it can obtain its own. In addition, GenBioPro's ANDA was not approved until 2019, meaning that GenBioPro has *never* operated under the regulatory regime that the Fifth Circuit purported to reinstate. Complying with the Fifth Circuit's judicial redlining of the FDA-approved product label may therefore require GenBioPro to purchase new equipment to create packaging and labels that it has never before used. Worse, the Fifth Circuit ordered these changes as a matter of *preliminary* injunctive relief, and thus the entire set of onerous changes could be reversed or altered after a final adjudication on the merits.

Until and unless this Court reverses the Fifth Circuit, the entire healthcare community will be wracked with confusion. GenBioPro's customers and partners will be faced with uncertainty about whether and how they can distribute and use mifepristone already circulating in the marketplace. And patients will be hindered in their ability to use mifepristone for medication abortion—even though their right to that care is protected by the law of most States. Those patients may be instead forced to undergo unnecessary *procedural* abortions, straining already overburdened healthcare facilities and clinics, all because a Fifth Circuit panel erroneously substituted its judgment for FDA's reasoned scientific decisionmaking.

This Court should reverse.[3]

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[3] This brief focuses on the Fifth Circuit's failure to properly consider and defer to FDA's scientific decisionmaking. GenBioPro concurs in Petitioners' other arguments, including that Respondents lack standing and that the Court should remand with instructions to dismiss on that basis.

ARGUMENT

I. The Fifth Circuit's Decision Disregards Decades Of Precedent Requiring Deference To FDA's Reasoned Scientific Decisions

The Fifth Circuit's opinion sets a dangerous precedent, and the court's cavalier departure from the most fundamental principles of APA review warrants reversal.

Two baseline precepts of APA review govern this case: (A) courts defer to expert agencies like FDA on questions of scientific judgment within the agency's expertise; and (B) courts reject an agency's scientific judgment only when it is clear *from the record before the agency* that the agency's decisionmaking was arbitrary and capricious. 5 U.S.C. § 706. The decision below ignored both requirements.

A. The Fifth Circuit's decision failed to grant the deference that this Court has long accorded to FDA's scientific and medical judgments, particularly those regarding questions of drug safety and effectiveness. See, *e.g.*, *Weinberger* v. *Bentex Pharms., Inc.*, 412 U.S. 645, 652-54 (1973) (emphasizing deference to FDA decisionmaking that depends on "administrative expertise," including the "expert knowledge and experience of scientists based on controlled clinical experimentation and backed by substantial support in scientific literature").[4]

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[4] See also, *e.g.*, *Young* v. *Cmty. Nutrition Inst.*, 476 U.S. 974, 981-82 (1986) (holding FDA's decision regarding safe levels of a toxin in feed for livestock intended for human consumption was entitled to "considerable deference" and was "sufficiently rational" to pass judicial review); *Cytori Therapeutics, Inc.* v. *FDA*, 715 F.3d 922, 923 (D.C. Cir. 2013) (Kavanaugh, J.) ("In [APA] cases alleging arbitrary and capricious agency action, courts must be careful not to unduly second-guess [FDA's] scientific judgments.").

The roots of this Court's deference to FDA's scientific judgments run far deeper than even the general admonition against courts "substitut[ing] [their] judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983); see *Merck Sharp & Dohme Corp.* v. *Albrecht*, 139 S. Ct. 1668, 1684-85 (2019) (Alito, J., joined by Roberts, C.J., and Kavanaugh, J., concurring) (FDA labeling determinations should be accorded "[t]he presumption of regularity [which] supports the official acts of public officers and, in the absence of clear evidence to the contrary, courts presume that they have properly discharged their official duties" (citation omitted)). This Court's deference to FDA's scientific determinations is also entirely separate from whatever deference may be owed to an agency's interpretation of a federal statute. Cf. *Chevron, U.S.A., Inc.* v. *Nat. Res. Def. Council, Inc.*, 467 U.S. 837 (1984).

Rather, because FDA's evaluation of patient safety and product efficacy derives from a wide array of complex medical evidence—including expert interpretation of clinical trial data, adverse event reports, and real-world postmarketing studies—courts are ill-equipped to scrutinize the agency's scientific judgments. See, *e.g.*, *S. Bay United Pentecostal Church* v. *Newsom*, 140 S. Ct. 1613, 1614 (2020) (Roberts, C.J., concurring in denial of application for injunctive relief) (cautioning against "second-guessing by an 'unelected federal judiciary,' which lacks the background, competence, and expertise to assess public health and is not accountable to the people" (citation omitted)). In the context of drug safety, as in other specialized technical matters, courts must "review scientific judgments of the agency not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality." *Troy Corp.* v.

Browner, 120 F.3d 277, 283 (D.C. Cir. 1997) (citation omitted).

This Court's insistence on deference to FDA's scientific judgments was exemplified most recently in a pair of orders issued in a challenge to FDA's handling of mifepristone distribution protocols during the COVID-19 pandemic. See *Am. Coll. of Obstetricians & Gynecologists* v. *FDA*, 472 F. Supp. 3d 183 (D. Md. 2020). In that case, a district court had enjoined FDA from enforcing a requirement that mifepristone dispensing occur only during in-person office visits. The court stressed that FDA had not provided any explanation for treating mifepristone differently from virtually all other drugs for which FDA had waived in-person dispensing requirements during the pandemic. *Id.* at 219. The government appealed the district court's order on an emergency basis.

On its first review, this Court held the case in abeyance, remanding "to permit the District Court to promptly consider a motion by the Government to dissolve, modify, or stay the injunction, including on the ground that relevant circumstances have changed." *FDA* v. *Am. Coll. of Obstetricians & Gynecologists* ("*ACOG I*"), 141 S. Ct. 10, 11 (2020). On remand, the government still did not submit a declaration from any federal official providing a justification for maintaining the in-person dispensing requirement solely for mifepristone. See *FDA* v. *Am. Coll. of Obstetricians & Gynecologists* ("*ACOG II*"), 141 S. Ct. 578, 584-85 (2021) (Sotomayor, J., dissenting). The district court reaffirmed its injunction. Despite the lack of *any* explanation of FDA decisionmaking in the record, this Court ruled for FDA, staying the district court's injunction against the in-person dispensing requirement. See *id.* at 578.

Across the two *ACOG* rulings, five Members of this Court wrote or joined opinions emphasizing the deference that reviewing courts *must* afford to FDA's safety and effectiveness conclusions, at least when they are supported by some reasoned analysis. See *id.* at 584 (Sotomayor, J., dissenting, joined by Kagan, J.) ("I agree that deference is due to reasoned decisions of public health officials grappling with a deadly pandemic."); *id.* at 579 (Roberts, C.J., concurring in the grant of application for stay) ("[M]y view is that courts owe significant deference to the politically accountable entities with the 'background, competence, and expertise to assess public health.'" (quoting *S. Bay United Pentecostal Church*, 140 S. Ct. at 1614 (Roberts, C.J., concurring in denial of application for injunctive relief))). Justices Alito and Thomas were especially critical of the district court's "second-guessing" of FDA's scientific judgments:

> [A] District Court Judge in Maryland took it upon himself to overrule the FDA on a question of drug safety. Disregarding the Chief Justice's admonition against judicial second-guessing of officials with public health responsibilities, the judge concluded that requiring women seeking a medication abortion to pick up mifepristone in person during the COVID-19 pandemic constitutes an "undue burden" on the abortion right, and he therefore issued a nationwide injunction against enforcement of the FDA's requirement.

ACOG I, 141 S. Ct. at 12 (Alito, J., dissenting, joined by Thomas, J.).

The separate opinions in *ACOG I* and *ACOG II* (collectively, "*ACOG*") could have been written for this case. In *ACOG*, as here, FDA's regulation of mifepristone was longstanding; the FDA decisions were based on complex scientific decisions regarding the same

prescription medication; and a single district judge issued a ruling with nationwide effect, disrupting the status quo. In *ACOG*, this Court reversed, holding that the district court erred by second-guessing FDA's scientific judgment rather than deferring. The same outcome is even more warranted here, where FDA had a robust scientific basis to support its agency action.

While the Fifth Circuit briefly noted the district court opinion in *ACOG*, Pet. App. 40a, it failed to acknowledge, much less analyze, any of these statements from the Justices in that case. But the end result in this case should be the same as in *ACOG*: reversal of preliminary relief disrupting the FDA's determinations and reinstatement of the status quo.

B. The Fifth Circuit's judgment also ignored the APA's record-review requirement by failing to await the full administrative record before radically altering the multi-year status quo based on purported concerns about the (unreviewed) record's contents. See Pet. Br. 36-38 (No. 23-236); *Am. Bioscience, Inc.* v. *Thompson*, 243 F.3d 579, 580 (D.C. Cir. 2001). This Court has long recognized the "settled proposition[]" that "a court is ordinarily limited to evaluating the agency's contemporaneous explanation in light of the existing administrative record." *Dep't of Com.* v. *New York*, 139 S. Ct. 2551, 2573 (2019); see *State Farm*, 463 U.S. at 43-44; *SEC* v. *Chenery Corp.*, 318 U.S. 80, 87 (1943). A thorough record-based review is even more important where, as here, the agency's determination turns on a large body of scientific literature and clinical studies; it is self-evident that such scientific determinations should not be set aside based only on a partial record in a preliminary-relief posture.

The courts below were fully aware that the record was incomplete, but chose to proceed anyway. In the district court, the parties agreed that adjudication of the plaintiffs'

preliminary injunction motion could be deferred until after the administrative record was produced. ROA 3240-3252, ROA 3588-3596, ROA 801-3811. But the district court declined to do so. ROA 4192. At oral argument in the Fifth Circuit, the panel suggested to counsel that the administrative record "seems like something we would want to know about," and asked whether the court needed the record prior to deciding the case. Oral Arg. at 24:06, *All. for Hippocratic Med.* v. *FDA*, 78 F.4th 210 (5th Cir. 2023) (No. 23-10362), https://bit.ly/45soBlV. Counsel for the government responded that "[you] absolutely need it." *Id.* at 22:52. Yet the court ruled without seeing anything but a highly abridged subset of that record.

While courts sometimes find it appropriate to stay or enjoin agency action to *preserve* the status quo, it turns administrative law upside down to *radically overhaul* the status quo under the guise of a "stay"—especially when the court lacks access to the administrative record upon which the agency based its longstanding decision. The lower courts' euphemistic labeling of their actions here as a mere "stay" (of administrative action that occurred years earlier) can hardly disguise the sweeping transformation being effected. See *Nken* v. *Holder*, 556 U.S. 418, 429 (2009) (noting stays generally are intended to "simply suspend judicial alteration of the status quo" (quoting *Ohio Citizens for Responsible Energy, Inc.* v. *NRC*, 479 U.S. 1312, 1313 (1986) (Scalia, J., in chambers))); *Turner Broad. Sys., Inc.* v. *FCC*, 507 U.S. 1301, 1302-03 (1993) (Rehnquist, C.J., in chambers); cf. *Benisek* v. *Lamone*, 138 S. Ct. 1942, 1945 (2018) ("[T]he purpose of a preliminary injunction is merely to preserve the relative positions of the parties until a trial on the merits can be held." (citation omitted)).

Tellingly, every case from this Court that the Fifth Circuit cited in its APA analysis involved review of a full

administrative record. Compare Pet. App. 51a-52a with *FCC* v. *Prometheus Radio Project*, 141 S. Ct. 1150, 1155 (2021) (rejecting challenge to FCC rule on full administrative record); *Michigan* v. *EPA*, 576 U.S. 743, 760 (2015) (emphasizing that APA review assesses "the grounds on which the agency acted"); *Marsh* v. *Or. Nat. Res. Council*, 490 U.S. 360, 369 (1989) (rejecting challenge to construction of dam after district court consolidated preliminary injunction motion with trial on the merits); *State Farm*, 463 U.S. at 43-44 (noting that "Congress required a record of the rulemaking proceedings to be compiled and submitted to a reviewing court").[5]

This Court afforded FDA deference in *ACOG* when the agency's explanation was essentially non-existent. Where, as here, FDA's decision is based on a robust scientific record, courts must at least examine that record before upending the multi-year status quo—especially when the costs and consequences of implementing the preliminary decision are not only severe, but might also prove entirely unnecessary if Petitioners prevail on remand.

In sum, the Fifth Circuit erred in failing to apply those fundamental precepts of APA review, and the magnitude

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[5] In describing the APA's arbitrary-and-capricious standard, the Fifth Circuit relied heavily on *Southwest Electric Power Co.* v. *EPA*, 920 F.3d 999 (5th Cir. 2019). But in that case, the court expressly *disclaimed* any intent to "question the scientific or statistical methodologies relied upon by EPA" or "second-guess its weighing of the statutory factors." *Id.* at 1022. Instead, it "rel[ied] on EPA's own scientific conclusions" and recognized that EPA was entitled to "special deference" in evaluation of "complex scientific data." *Id.* (quoting *BCCA Appeal Grp.* v. *EPA*, 355 F.3d 817, 824 (5th Cir. 2003)); see Pet. App. 52a-53a, 55a, 61a, 63a. And the rulings that the partial concurrence cited for invalidation of FDA decisions likewise focused on legal issues; none purported to reverse FDA's scientific or medical judgments. See Pet. App. 108a-109a.

of its departure from settled precedent illustrates the need for reversal.

II. The Fifth Circuit's Likelihood-of-Success Determinations On An Incomplete Preliminary Record Are Badly Flawed

Without an administrative record, it is no surprise that the reasoning the Fifth Circuit offered for its partial "stay" of FDA's changes to mifepristone's conditions of use reflects a fundamental misunderstanding of the scientific data underlying and fully justifying the Agency's decisions.

The Fifth Circuit held that the 2016 modifications to the mifepristone use conditions (the "2016 Modifications") were likely arbitrary and capricious because FDA failed to consider their "cumulative effect" and because FDA revised its prior mandate that all doctors directly report any non-fatal adverse events to the Agency. Pet. App. 52a-55a. The Fifth Circuit also found that FDA likely acted unlawfully in its 2016 and 2021 decisions to rescind the three-office-visits protocol for mifepristone use because FDA overly credited adverse-event data in its Adverse Event Reporting System (FAERS) and relied on studies that the Agency purportedly admitted were inconclusive. Pet. App. 60a-63a.

Each of the Fifth Circuit's conclusions was wrong. Even the limited portions of the record available to the lower courts demonstrated—and the full administrative record would have confirmed—that FDA reviewed and properly analyzed voluminous data on the safety of the each of the proposed changes.

A. FDA's Decisions To Extend The Use Period From Seven To Ten Weeks And Rescind The Office-Visits Protocol Were Fully Supported

At the outset, the Fifth Circuit failed to properly credit the strong scientific bases for FDA's decisions,

flouting this Court's deference to the Agency's safety determinations.

First, the Fifth Circuit ignored that the 2016 change to the label increasing the period in which mifepristone can be used from seven to ten weeks was grounded in FDA's extensive 2016 Medical Review, which found that the extension was supported by 19 clinical studies involving more than 35,000 patients—all showing remarkable efficacy, in the range of 89-98%, with only "rare" side effects of any kind. ROA 2327-2332; see J.A. 398 ("Our review of this postmarketing data indicates that there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced."). That sort of scientific analysis is precisely what Congress envisioned, and it far exceeds the minimum standard of rationality that the APA requires. See *State Farm*, 463 U.S. at 52 ("The agency must explain the evidence which is available, and must offer a rational connection between the facts found and the choice made." (citation omitted)). Indeed, the Fifth Circuit did not and could not dispute any of the Agency's findings on the use period given that, of the 19 supporting studies that FDA examined, ROA 2327-2332 (summary chart of studies FDA relied upon), only one (Winikoff 2012, ROA 727-733) was available in the record below.

The Fifth Circuit similarly failed to credit the wealth of scientific data FDA reviewed in its 2016 and 2021 decisions rescinding the three-office-visit protocol for mifepristone. FDA compiled and analyzed a robust record addressing those changes and repeatedly found that the data confirmed their safety. With respect to the second visit, FDA relied in 2016 on studies involving "large numbers of women in the U.S. who took misoprostol at

home," which found "exceedingly low rates of serious adverse events." J.A. 308. The Agency further found that "allowing home administration [of misoprostol] increases the likelihood that a woman will be in an appropriate and safe location when the pregnancy termination process begins." J.A. 309; see also ROA 2320-2324 (listing supporting studies).

For the third, "follow-up" visit, FDA similarly found that several clinical studies and a "systematic article" surveying the literature established that "there were no significant differences in adverse outcomes between women who underwent self-assessment of health compared to those who had a clinic visit." J.A. 309. Here, FDA outlined 11 studies, involving more than 50,000 patients, that supported its decision. ROA 2306-2309; see ROA 2332-2334.

Further, when FDA decided in April 2021 to exercise discretion not to enforce the in-person dispensing requirement during the COVID-19 public health emergency, it cited four new studies (released after 2016) that found no "increases in serious safety concerns" with waiving in-person dispensing among the thousands of patients who used various telehealth programs. J.A. 364-365. Each of the studies—which were cited but not provided in the record before the Fifth Circuit—involved dispensing of mifepristone up to ten weeks, at the lower dosage adopted in the 2016 Modifications, and without any office visits.[6]

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[6] J.A. 364-365 & n.1 (citing Erica Chong et al., *Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic*, 104 Contraception 43 (2021), https://bit.ly/3SlV3l8; Courtney Kerestes et al., *Provision of medication abortion in Hawai'i during COVID-19: Practical*

Finally, in its December 2021 response to a citizen petition seeking to reinstate a *three*-office-visit protocol, FDA similarly conducted a thorough review of the adverse event data from telehealth provision of mifepristone following the April 2021 non-enforcement announcement. J.A. 384-390, 397-408. Reaffirming the 2016 Modifications and April 2021 decision, FDA found that "there have not been any new safety concerns" with mifepristone use through ten weeks and without office visits, concluding that "mifepristone may be safely used without in-person dispensing." J.A. 398-400 (citing 12 studies).[7]

Once again, the Fifth Circuit's ruling ignored this solid track record of scientific decisionmaking. It did not conduct its own review of the extensive evidence FDA relied on for the changes. Nor could it: Not one of the four studies relied upon by FDA for its April and December 2021 decisions was in the woefully incomplete record before the court.

Instead, the Fifth Circuit reimposed the pre-2016 office-visits regime, including in-person dispensing, based

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experience with multiple care delivery models, 104 Contraception 49 (2021), https://bit.ly/497RTs0; ARA Aiken et al., *Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study*, 128 BJOG 1464 (2021), https://bit.ly/3HBoYkw; John Joseph Reynolds-Wright et al., *Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic*, 47 BMJ Sexual & Reprod. Health 246 (2021), https://bit.ly/3UjtOdB).

[7] In January 2023, FDA formally modified the mifepristone REMS to permanently remove the in-person dispensing requirement based on its conclusion, after reviewing even more updated data, that "no new safety concerns [have been] identified" since the December 2021 response. See Ctr. for Drug Evaluation & Rsch., *Approval Package for: Application Number: 020687Orig1s025*, at 68 (Jan. 3, 2023), https://bit.ly/3SlTe83. Respondents have not challenged FDA's January 2023 modification in this case.

on a statement in FDA's December 2021 decision that mifepristone's adverse event profile was based, in part, on studies which varied somewhat in their design. Pet. App. 61a-62a; J.A. 400. But the court failed to add that, in a seven-page discussion immediately following that comment, FDA proceeded to detail the results of ten studies, involving thousands of patients, that demonstrated the safety of mifepristone when dispensed in a wide range of settings (including retail pharmacies, mail-order pharmacies, couriers, and Internet providers), all without any in-person visits. J.A. 401-408. In this respect, the Fifth Circuit went beyond "second-guessing" the Agency's judgments, instead ignoring FDA's well-supported reasoning entirely.

B. The Fifth Circuit Misconstrued FDA's Analysis And Demanded Unprecedented And Unscientific Requirements For The Agency's Decisionmaking

Despite acknowledging that "FDA is not required to conduct a study that perfectly mirrors the conditions under which the drug will be used," the Fifth Circuit held that the 2016 Modifications were arbitrary and capricious because FDA supposedly failed to consider their "cumulative" effects. Pet. App. 53a-54a. But because FDA concluded that *each* of the changes in the 2016 Modifications was safe—conclusions the Fifth Circuit did not question—there is no reason to assume that the "cumulative" effects of the changes would provide any cause for concern, let alone to the degree necessary to overturn the Agency's expert judgment. The Fifth Circuit's opinion provides no reasoned basis for its contrary conclusion, instead declaring without citation that the "cumulative effect" was "unquestionably an important aspect of the problem" before the Agency. Pet. App. 53a.

Tellingly, the Fifth Circuit did not cite the statute governing the REMS program, nor any FDA regulations or prior Agency practice, nor any case law, for its view that modifications to use conditions for drugs subject to a REMS must be supported by an all-in-one analysis that simultaneously examines every element of some proposed set of changes. None exists.

In fact, the court's approach is squarely at odds with the REMS statute and FDA's implementing guidance that governed its decisionmaking. Congress provided that a REMS is to be based on *any* "new safety information" and listed a range of data sources, many of which go beyond clinical studies. 21 U.S.C. § 355-1(a)(2)(A) (permitting post-approval REMS based on "new safety information"); see *id.* § 355-1(b)(3) (broadly defining "new safety information" to include adverse event reports, postapproval studies, postmarket data or "other scientific data deemed appropriate by the Secretary"). Far from requiring an all-in-one study, Congress thus expressly authorized FDA to devise a REMS program based on the Agency's own analysis of a broad array of disparate data.

FDA's REMS guidance documents reflect that authorization, stating that the requisite "adequate rationale" for a REMS modification "may include" a wide range of information on "the reason(s) why the proposed modification is necessary; the potential effect of the proposed modification on how the REMS addresses the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the healthcare delivery system; and other appropriate evidence or data to support the proposed change." FDA, *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* 12 (June 2020), https://bit.ly/4brGJ3A; see also FDA, *REMS Assessment:*

Planning and Reporting 4, 8-12 (January 2019), https://bit.ly/3SAZnOO.

Even though the Fifth Circuit proclaimed that "[t]he problem is not that FDA failed to conduct a clinical trial that included each of the proposed changes as a control," Pet. App. 54a, it effectively required exactly that. But here, the congressionally mandated standard for modifying a REMS provision does not require *any* clinical studies. And, even if it did, "determining whether a study is adequate and well controlled" is precisely the kind of specialized judgment that Congress has entrusted to the Agency. See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 621 & n.17 (1973). The Fifth Circuit's contrary analysis ignored the applicable standard and failed to defer to FDA's reasoned scientific determinations.

The Fifth Circuit's other basis for finding the 2016 Modifications likely invalid was equally unfounded. The court held that FDA lacked grounds for removing a REMS provision that had required doctors to report directly to the FAERS any adverse event following use of mifepristone (retaining mandatory reporting only for deaths). Pet. App. 54a-56a. That finding was error.

The court began its discussion of the FAERS issue by acknowledging that FDA had, in fact, expressly addressed and explained that change in its 2016 REMS decision, Pet. App. 54a—a "rational explanation" that alone should have ended the matter under *State Farm*. Indeed, the court acknowledged that the FDA review officer had specifically found (with numerous citations) that the change in adverse event reporting was appropriate because "after 15 years of reporting serious adverse events" using the mandatory program solely for mifepristone, "the safety profile for [mifepristone] is essentially unchanged." Pet. App. 54a.

The Fifth Circuit dismissed those 15 years of specialized agency experience by speculating that the other changes made in the 2016 Modifications "might alter the risk profile." Pet. App. 55a. Again, the Fifth Circuit did not offer any factual support for its speculation on that scientific question. Nor did the court cite anything in any statute, regulation, or prior decision to authorize a reviewing court to "second-guess" FDA on the optimal way to acquire and examine adverse event reports for any drug. No such authority exists.

In reality, FDA's decision to remove mifepristone prescribers' obligation to report non-fatal adverse events was consistent with its policy and practice as to virtually all other drugs. For decades, FDA's MedWatch and FAERS programs have relied on *voluntary* reporting by physicians who *may* submit such reports *as they see fit* to manufacturers, distributors, or directly to FDA.[8] Indeed, this reporting process is voluntary even for the vast majority of drugs subject to REMS programs. The only drugs for which FDA *requires* prescribers to report adverse events are a small subset of REMS drugs; and, typically, that reporting requirement is only for fatal adverse events.

Despite that context, the Fifth Circuit concluded that FDA somehow violated the APA when it rescinded the requirement that mifepristone prescribers report *all* adverse events and instead required only reports of *fatal* adverse events. That modification is consistent with how other REMS drugs are treated and leaves in place a regime that is still more rigorous than the one FDA uses for the vast majority of approved drugs. Pet.App. 55a-56a. In this respect, the Fifth Circuit's decision was not so

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[8] See 87 Fed. Reg. 14,895 (Mar. 16, 2022) (describing voluntary nature of MedWatch reporting for health care professionals); 78 Fed. Reg. 68,844 n.51 (Nov. 15, 2013) (same for FAERS).

much a judicial *review* of the 2016 Modifications as a flat-out rejection from the outset of FDA's reasoned decisionmaking.

Even if there were some merit to the Fifth Circuit's view, the court failed to explain why that view justified invalidating the *entirety* of the 2016 Modifications. At most, inadequate reasoning on adverse event reporting might support vacating the altered reporting obligation—but no more. Any doubts about a *prospective* change to data-collection practices could not logically undermine the safety and efficacy findings FDA made for the other 2016 Modifications, which necessarily were based on data already in FDA's possession.

By disregarding and misreading the robust record supporting FDA's decisionmaking, and imposing requirements on the agency with no scientific or doctrinal basis, the Fifth Circuit substituted its judgment for the Agency's. The court's cascading series of errors merit swift reversal.

III. The Fifth Circuit Disregarded Statutory Requirements For REMS Modifications

Beyond its failure to defer to FDA's reasoned scientific judgments, the Fifth Circuit also ignored the statutory standards for REMS modifications, which require consideration of the *benefits* of proposed modifications—in particular, assuring patient access-—alongside any potential drawbacks. FDA properly followed those standards in its decisions to modify the mifepristone REMS. The Fifth Circuit's determination that those decisions were arbitrary and capricious—without evaluating them in light of the "factors which Congress … intended [the Agency] to consider," *State Farm*, 463 U.S. at 43—was error.

In the REMS statute, Congress directed FDA to include "elements to assure safe use" (sometimes called

"ETASU") in certain REMS programs. 21 U.S.C. § 355-1(f)(2). Importantly, when imposing such elements, FDA must weigh two competing interests: "[p]roviding safe access for patients" on the one hand, and "assur[ing] safe use of the drug" on the other. *Id.* § 355-1(f), (f)(1). Indicating its intended balance, Congress further specified that elements to assure safe use must "not be unduly burdensome on patient access to the drug," and, "to the extent practicable," must "minimize the burden on the health care delivery system." *Id.* § 355-1(f)(2)(C)-(D). Congress was particularly concerned about access to REMS drugs for "patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)." *Id.* § 355-1(f)(2)(C)(ii). To ensure consistency with the statute's priorities over time, Congress required FDA to "periodically evaluate" all elements to assure safe use "to assess whether" they continue to "assure safe use," "are not unduly burdensome on patient access," and "to the extent practicable, minimize the burden on the health care delivery system." *Id.* § 355-1(f)(5)(B).

FDA adhered carefully to Congress's mandate and correctly weighed both access and safety in its modifications to the REMS. For example, with respect to its 2021 decision that in-person dispensing of mifepristone is unnecessary, FDA concluded, in its December 2021 response to the citizen petition, that "to reduce the burden imposed" by the REMS, the program "must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies," dramatically improving patient access. J.A. 407; see also *id.* ("Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients."). FDA further concluded that "mifepristone will remain safe and effective if the in-

person dispensing requirement is removed," reaching that determination based on (a) a review of data from an assessment of the REMS between 2019 and 2020; (b) adverse event data from FAERS from the period in which the in-person dispensing requirement was waived; and (c) the latest literature. J.A. 407; see J.A. 397 & n.77.

In rejecting the REMS modifications as arbitrary and capricious, the Fifth Circuit mentioned neither the REMS statute's balancing mandate, nor the reasoned findings by the Agency that expressly satisfied Congress's requirements.

To be sure, the court acknowledged that "public-interest considerations" weighed against granting preliminary relief, including an argument by public-health group *amici* that disrupting access to mifepristone "would burden state and local health-care systems." Pet. App. 67a-68a. But the court erroneously minimized those "not insignificant" concerns as applying "primarily (if not wholly)" to Respondents' challenge to the initial mifepristone approval in 2000. Pet. App. 67a. The court reasoned that, to the extent those concerns bear on the 2016 and 2021 decisions, "they are lessened by the fact that mifepristone would remain available under the 2011 REMS." *Id.* That statement lays bare the court's failure to acknowledge—let alone meaningfully consider—the REMS statute's mandate, or to appreciate the FDA's reasoning that properly applied it.

The Fifth Circuit never explained how the goal of "safe access" that Congress mandated, which FDA considered in the 2016 and 2021 decisions, would not be significantly hampered by reversion to the pre-2016 regime. 21 U.S.C. § 355-1(f). Nor did the court consider the reasonableness of FDA's decisionmaking in carrying out the REMS statute's requirements. In examining agency action, the reviewing court's role is to assess

"whether the [agency's] decision was 'based on a consideration of the relevant factors and whether there has been a clear error of judgment.'" *DHS* v. *Regents of Univ. of Cal.*, 140 S. Ct. 1891, 1905 (2020) (quoting *Citizens to Preserve Overton Park, Inc.* v. *Volpe*, 401 U.S. 402 (1971)). The Fifth Circuit could hardly evaluate the lawfulness of the REMS modifications without examining FDA's "consideration of the relevant factors" that Congress set out in the REMS statute. *Id.* By ignoring both the governing statutory directive and the Agency's reasoned implementation, the Fifth Circuit committed another serious error that warrants reversal.

IV. The Fifth Circuit's Decision Will Significantly Harm GenBioPro And The Public Interest

A. The Fifth Circuit acknowledged the "significant injury" that its decision stands to cause to Danco, the brand-name manufacturer of mifepristone. Pet. App. 66a. As Danco has explained, it faces the threat of having its product "effectively remove[d] … from the market for an unknown length of time" while it may be forced to pursue renewed regulatory approval for a label that describes antiquated and unscientific methods of administration—including a dose *three times* the current dosing regimen of 200 mg—and that may itself be superseded by a different final judgment. Pet. Br. 18-19 (No. 23-236); see *id.* at 53-54.

GenBioPro faces those same threats, but to an even greater degree. If the Fifth Circuit's decision stands, GenBioPro may need to immediately stop selling its product because the current, approved labeling would instantly become inconsistent with the pre-2016 protocol forced into effect by that court. 21 U.S.C. § 355(a). Because mifepristone and misoprostol are GenBioPro's only products, and because mifepristone constitutes 95% of GenBioPro's business, that result would portend

catastrophic financial and operational distress and put in question GenBioPro's continued viability.[9]

Importantly, the potential harm is even greater for GenBioPro than Danco because GenBioPro's reapproval likely would lag behind Danco's. As the generic manufacturer, GenBioPro's label must match Danco's exactly, 21 U.S.C. § 355(j)(4)(G); 21 C.F.R. §§ 314.94(a)(8)(iii), 314.150(b)(10), meaning GenBioPro would need to wait for FDA approval of Danco's new labeling before GenBioPro could obtain approval. See *Mut. Pharm. Co.* v. *Bartlett*, 570 U.S. 472, 477 (2013).

In addition, if implementing the Fifth Circuit's decision requires regressing to the 600 mg regimen for mifepristone in the pre-2016 label—which was abandoned years before GenBioPro obtained approval for its generic drug, Pet. App. 10a—GenBioPro would need to redesign its entire manufacturing process. That would necessitate purchasing and certifying new production equipment to produce a three-tablet blister pack that GenBioPro has never before sold. GenBioPro would also need to redesign the product label and physical packaging. In addition to the necessary capital costs, these steps would further delay GenBioPro's market reentry and ability to regain its predominant stream of revenue.

Even after GenBioPro's return to the market, it would lose the substantial portion of its sales accounted for by pharmacies and providers that engage in mail-order and telemedicine prescriptions. And across all of GenBioPro's current customers and partners, the Fifth Circuit's

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[9] Illustrating the unusual nature of its novel "stay" remedy, the Fifth Circuit held that the plaintiffs lacked standing to challenge GenBioPro's 2019 ANDA approval, Pet. App. 42a-44a, while at the same time issuing a ruling that would fundamentally alter GenBioPro ANDA rights by potentially subjecting it to all aspects of the Fifth Circuit's newly imposed REMS regime.

opinion creates a cloud of uncertainty over the legal status of existing inventory, especially inventory in the hands of distributors, dispensers, and patients. The utterly unprecedented nature of court-ordered changes to an approved drug label for products that are already in the stream of commerce threatens confusion and turmoil for all entities and individuals that purchase, distribute, prescribe, and use mifepristone.

B. Beyond the harm to GenBioPro and its partners, customers, and affiliates, the Fifth Circuit's decision would impose immense harm on patients and health care providers across the country. The Fifth Circuit proceeded with its "stay" despite having been informed that, to the extent the decision eliminates or substantially restricts access to mifepristone, even temporarily, it "may pose health risks to certain women, including those who use the drug to manage miscarriage," and will burden state and local health care systems. Pet.App. 67a-68a.

Without mifepristone, patients in need of abortions may be forced to seek procedural abortions or may be forced to carry pregnancies to term against their will. While procedural abortion is safe, it involves anesthesia, which can carry its own complications. Procedural abortion is also more difficult to access than medication abortion, particularly for patients in rural and underserved communities who face the most obstacles to obtaining care.

There are also significant practical consequences to the specific changes the Fifth Circuit mandated. For one thing, its ruling reduces the approved period for mifepristone use from ten weeks to seven—a point in time when a substantial percentage of patients do not know they are pregnant. See Amy M. Branum & Katherine A. Ahrens, U.S. Ctrs. for Disease Control, *Trends in Timing of Pregnancy Awareness Among US Women*, 21 Maternal

& Child Health J. 715 (2017), https://bit.ly/3ueCKXd (finding mean time of unintended pregnancy awareness was 5.7 weeks for all Americans and 7.4 weeks for those 15 to 19 years old). In addition, as FDA recognized, requiring in-person dispensing would make it extremely difficult for many patients to access mifepristone. And for patients who can access mifepristone, the pre-2016 labeling would instruct them to take three times the medically required dosage, which is out of step with the current standard of care.

The Fifth Circuit did not even attempt to assess the harm to patients and the burden on the health care system of reverting to these outdated conditions of distribution and use. Instead, the court justified its decision by declaring that its effects would be comparatively less harmful than revoking the drug's approval altogether. Pet. App. 66a. The fact that the court (correctly) rejected the most extreme outcome does not excuse it from examining the harms and burdens that would flow from the decision it did reach. And in any event, FDA itself carefully considered the potential harm and benefits to patients when making its decisions, and it determined the changes were appropriate. The Fifth Circuit provided no reasoned basis to depart from those conclusions.

In myriad ways, the Fifth Circuit's reasoning evinces a profound failure to grapple with the cascading harms its ruling will cause. While the court recognized that its judgment would cause "significant injury," it fell back on this Court's stay of its decision as mitigating those concerns. Pet. App. 66a-68a. But unless this Court reverses the Fifth Circuit's decision, this Court's stay will have only *delayed* the harm. And because the Fifth Circuit has ordered affirmative relief at the preliminary-injunction stage, all of the steps that mifepristone manufacturers and their partners, customers, and

patients would take in response to the Fifth Circuit's judgment taking effect could be completely wasted efforts if FDA and Danco eventually prevail on remand, requiring both Danco and GenBioPro to then switch their processes back to those in effect before the lower courts' drastic preliminary orders. None of those wasteful steps will be necessary, and all of these harms will be avoided, if the Fifth Circuit judgment never takes effect.

CONCLUSION

The Fifth Circuit's judgment should be reversed.

Respectfully submitted.

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