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 PETITIONS FOR 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 on the sale of mifepristone will have substantial effects on GenBioPro's business.

Mifepristone is subject to a special set of FDA requirements 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 that FDA approved for mifepristone in 2016—three years before FDA approved GenBioPro's ANDA and GenBioPro began selling the drug. The decision 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 even potentially for products already in the stream of commerce. And because the decision below is preliminary in nature, efforts to comply with the changed regulatory scheme

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[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. All parties were given timely notice of this filing.

would all be wasted if any court rules differently on remand.

If the Fifth Circuit's decision stands, GenBioPro will be unable to sell mifepristone until making the significant changes to its product and marketing practices that would be necessary to comply with the pre-2016 conditions and obtain FDA approval of those changes. Because GenBioPro holds a generic approval, it would not be able to seek approval until the brand-name manufacturer—Petitioner Danco Laboratories, L.L.C.—first receives approval for its own labeling change. And even after GenBioPro's product is approved, the market to which it regains access will not resemble any status quo ante because, under the Fifth Circuit's decision, 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, and the patients it serves that would result if the Fifth Circuit's decision remains in force.

INTRODUCTION AND SUMMARY OF ARGUMENT

On April 21, 2023, 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 American women for more than two decades.[2] The Fifth Circuit's decision here engages in further judicial second-guessing, affirming the district court's purported "stay" of FDA's scientific judgment—which was based on years of experience and analysis of clinical research and

[2] Except where noted, this brief references the Petition and the Petitioner's Appendix filed by FDA in No. 23-235.

other safety data—that certain restrictions on mifepristone were not necessary for its safe use. Pet. App. 4a.

The Fifth Circuit's second-guessing of FDA violated fundamental principles of judicial review under the Administrative Procedure Act ("APA"). It refused to accord the deference that this Court has repeatedly 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 evidence on which FDA 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, finding that it had improperly interfered with FDA's decisionmaking on one of the same safety 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, 584-85 (2021). Without even acknowledging those rulings, the Fifth Circuit brazenly overrode FDA decisionmaking on the *same issue*, disrupting the status quo, and doing so based on a deeply flawed analysis of an incomplete record.

The Fifth Circuit's opinion demonstrates the wisdom of this Court's warning against judicial interference with FDA's reasoned scientific determinations—particularly on an incomplete record. For instance, the Fifth Circuit did not question FDA's determination that every individual aspect of its 2016 modifications to the REMS ensured that mifepristone remained a safe and effective drug. Yet without citing any evidence or record support, the Fifth Circuit speculated that the "cumulative" effect of those modifications *could* be unsafe, calling this an "important aspect of the problem." Pet. App. 54a.

In fact, the court never even examined the clinical studies underlying and amply supporting FDA's 2016 REMS changes. Without the administrative record, it is unclear how the Fifth Circuit could have determined what scientific evidence FDA may have "failed to consider." 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 Fifth Circuit's judgment was egregiously wrong, and this Court should not allow it to stand.

The real-world consequences of the Fifth Circuit's erroneous ruling are severe. The court recognized that its holding would cause "significant injury" to Danco, which will be prohibited from selling any of its existing product, Pet. App. 66a, until it obtains FDA approval for revised labeling. And GenBioPro will endure those harms to an even greater degree. Because the labeling for its generic mifepristone must match Danco's precisely, GenBioPro must 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 *only* operated under the REMS requirements the Fifth Circuit purported to "stay." Complying with the Fifth Circuit's judicial redlining of the FDA-approved product label would require GenBioPro to purchase new equipment to create packaging and labels that it has never before used. Worse, the Fifth Circuit required these changes as a matter of *preliminary* injunctive relief, and thus the entire set of onerous mandated changes could be reversed or altered after a final adjudication on the merits.

In the interim, 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 in some form by the constitutions or statutes 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 grant certiorari and reverse.[3]

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 offhand departure from the most fundamental principles of APA review warrants this Court's intervention.

Two baseline precepts of APA review should 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 opinion 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 regarding questions of drug safety and effectiveness. See, *e.g.*, *Weinberger* v. *Bentex Pharms., Inc.*, 412 U.S. 645, 652 (1973) (emphasizing deference to FDA decisionmaking

[3] This brief focuses on the Fifth Circuit's failure to properly consider and defer to FDA's scientific decisionmaking. GenBioPro shares Petitioners' views that the issues of standing also warrant review.

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]

The roots of this Court's deference to FDA run far deeper than even the generalized 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 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 simply ill-equipped to scrutinize the agency's scientific judgments. See, *e.g.*, *S. Bay United Pentecostal Church* v. *Newsom*, 140 S. Ct.

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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.").

1613, 1614 (2020) (Roberts, C.J.) (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.* 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

administration requirement solely for mifepristone; and the district court reaffirmed its injunction. See *FDA* v. *Am. Coll. of Obstetricians & Gynecologists* ("*ACOG II*"), 141 S. Ct. 578, 584-85 (2021) (Sotomayor, J., dissenting). But despite the lack of any documented FDA decisionmaking in the record, this Court ruled for FDA, staying the district court's injunction against the in-person dispensing requirement. See *id.*

In the *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":

> [A] District Court Judge in Maryland took it upon himself to overrule 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., joined by Thomas, J., dissenting).

The separate opinions in *ACOG I* and *ACOG II* (together, "*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*, the Court reversed, holding that the district court erred by second-guessing FDA's scientific judgment rather than deferring.

The Fifth Circuit failed to acknowledge any of these statements from the Justices in the *ACOG* decisions. But the end result in this case should be the same as in *ACOG*: reversal of preliminary relief disrupting the FDA's scientific judgments and reinstatement of the status quo pending further litigation on remand.

B. The Fifth Circuit's judgment also ignored the APA's record-review requirement by refusing 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. 4, 30-31 (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; *SEC* v. *Chenery Corp.*, 318 U.S. 80, 87 (1943). A thorough record-based review is even more important where 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 plaintiffs' preliminary injunction motion could be deferred until after the administrative record was produced. ROA.3240-3252, ROA.3588-3596, ROA.3801-3811. But, the district court declined to do so. ROA.4192. In questions to counsel at oral argument, the Fifth Circuit likewise suggested that the administrative record "seems like something we would want to know about," yet the court ruled without ever seeing anything but a highly abridged subset of that record. 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.

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 issuing a "stay." This is especially true when the court lacks access to the administrative record upon which the agency based its decision. The lower courts' euphemistic labeling of their actions 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 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").

As illustrated by *ACOG*, even when FDA's reasoning is essentially non-existent, courts must defer to the Agency's scientific judgment, particularly where doing otherwise will disrupt the status quo. 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 eventually prevail on remand.

In sum, the Fifth Circuit erred in failing to apply those fundamental precepts of APA review, and the sheer magnitude of its departure from settled precedent warrants this Court's intervention.

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" reflects a fundamental misunderstanding of the scientific facts underlying FDA's decisions.

Specifically, the Fifth Circuit held that the 2016 modifications to the mifepristone REMS (the "2016

REMS Modifications") were likely arbitrary and capricious because FDA failed to consider their "cumulative effect" and because FDA eliminated its prior mandate that all doctors directly report any non-fatal adverse events to the Agency. Pet. App. 52a-55a. The Fifth Circuit also held FDA's 2016 and 2021 decisions, which together eliminated the three-office-visits requirement, were unlawful because FDA overly credited adverse-event data in the FDA's Adverse Event Reporting System (FAERS) and relied on studies that the Agency purportedly admitted were inconclusive. Pet. App. 60a-63a. Each conclusion was wrong.

A. To begin, the Fifth Circuit found no fault in FDA's review or analysis of the data supporting any *individual* modification to the REMS. Pet. App. 52a-55a. Nor could it. Even the limited portions of the record available demonstrate that FDA reviewed voluminous data on the safety of the proposed REMS modifications.

For example, in deciding to increase the period in which mifepristone could be used from 7 to 10 weeks, FDA relied on its extensive 2016 Medical Review, which found that the extension was supported by 22 clinical studies involving 35,000 patients—all showing remarkable efficacy, in the range of 91-98%, with only "rare" side effects of any kind. ROA.2170-2180; see ROA.828 ("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 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. *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 given that, of the 34 studies FDA summarized in its 2016 decision to support its extension of the use period and elimination of the second and third office visits, ROA.2320-2324, ROA.2327-2334, only one (Winikoff 2012, ROA.727-733) was available in full in the record on appeal.

In reaching its contrary conclusion, the Fifth Circuit acknowledged that "FDA is not required to conduct a study that perfectly mirrors the conditions under which the drug will be used," yet nonetheless insisted that FDA failed to consider the "cumulative" effects of the 2016 REMS Modifications. Pet. App. 53a-54a. But because FDA concluded that *each* of the changes in the 2016 Modifications was safe and would ensure that the benefits of the drug outweigh the risks—and because the court found no flaw in those analyses—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 answer, 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, FDA regulations, or prior agency practice for its view that a REMS modification must be supported by an all-in-one analysis that simultaneously examines every element of some proposed set of changes. The REMS statute provides that a REMS is to be based on *any* "new safety information" and lists 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"). Congress plainly authorized FDA to adopt REMS requirements based on the Agency's own analysis of a broad array of disparate data. FDA's implementing guidance documents reflect that authorization, making clear that both an initial REMS and any modifications *must* reflect all forms of existing data, including patient experience, in addition to clinical studies. FDA, *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* 12 (June 2020), https://bit.ly/46KpZkY; FDA, *REMS Assessment: Planning and Reporting* 4, 8-12 (January 2019), https://bit.ly/3FcmUOM.

In other words, even though the court 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 ignores the applicable standard and fails to defer to FDA's scientific determinations.

B. The Fifth Circuit's other reason for finding the 2016 REMS Modifications likely invalid was equally novel. The court held that FDA erred in 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.

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.

But the Fifth Circuit nonetheless dismissed those 15 years of specialized agency experience by speculating that the other changes made in the 2016 REMS 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 events with any drug. No such authority exists.

In reality, FDA's decision to remove mifepristone prescribers' obligation to report non-fatal adverse events was entirely 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.[5] Indeed, this is true even for the 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

[5] 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).

context, the Fifth Circuit concluded that FDA somehow violated the APA when it eliminated 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 what FDA uses for the vast majority of approved drugs. Pet. App. 55a-56a. Thus, the court's decision was not so much a judicial *review* of the 2016 REMS Modifications as a flat-out rejection 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 *entire* 2016 REMS 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.

C. The Fifth Circuit's purported stay of FDA's 2016 and 2021 decisions, which together eliminated the three-office-visits requirement for mifepristone patients, likewise flouted this Court's deference to FDA safety determinations. FDA compiled and analyzed a robust record for both the 2016 and 2021 decisions, repeatedly finding that the safety of eliminating in-office requirements was confirmed by the scientific data.

The 2016 REMS Modifications eliminated the second (misoprostol administration) and third (follow-up) office visits. With respect to the second visit, FDA relied on recent studies involving "large numbers of women in the U.S. who took misoprostol at home," which found "exceedingly low rates of adverse events." ROA.713. 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." ROA.714.

Turning to the third, "follow-up" visit, FDA noted the lack of any safety rationale for follow-up clinic visits. ROA.714. Here, FDA outlined 11 studies, involving more than 50,000 patients, supporting its decision. ROA.2306-2309.

In April 2021, when FDA decided to exercise discretion not to enforce the initial in-person dispensing office visit during the COVID-19 public health emergency, it examined several new studies released after 2016 that found no "increases in serious safety concerns" with waiving in-person dispensing. ROA.787-788.

And in its December 2021 response to a citizen petition seeking to reinstate *all three* office visits, FDA conducted a thorough review of the adverse event data from the telehealth prescription of mifepristone following the April 2021 non-enforcement announcement. ROA.814-820, 827-838. It concluded that "mifepristone may be safely used without in-person dispensing." ROA.829.[6]

The court'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 its determinations. Nor could it; again, not one of the studies

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[6] In January 2023, FDA formally modified the REMS to permanently remove the initial in-person dispensing visit 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/48Qdwha. Respondents have not challenged FDA's January 2023 modification in this case.

relied upon by FDA for its April and December 2021 decisions were in the woefully incomplete record before the court.[7]

Instead, the Fifth Circuit reimposed the pre-2016 requirement for three separate office visits based 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; ROA.830. But the court failed to add that, in a seven-page discussion following that snippet, FDA proceeded to detail the results of ten studies, involving thousands of patients, demonstrating 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 physician visits. ROA.831-838.

In this respect, the Fifth Circuit did not so much "second-guess" a reasoned and well-supported FDA analysis as ignore it entirely, substituting its own judgment for the Agency's. The Fifth Circuit's cascading series of errors merits this Court's review.

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

A. The Fifth Circuit recognized the "significant injury" that its decision would cause to Danco, the brand-name manufacturer of mifepristone. Pet. App. 66a. As Danco explains in its petition, "the decision below will remove [Danco's product] Mifeprex from the market entirely for an extended period of time" while Danco pursues renewed regulatory approval for a label describing antiquated and unscientific methods of

[7] FDA cited four studies in April 2021, ROA.787, and 12 additional studies in December 2021, ROA.829-838.

administration, including a dose *three times* the current dosing regimen of 200 mg. Pet. 36 (No. 23-236).

GenBioPro faces those same injuries, but to an even greater degree. Like Danco, GenBioPro would need to immediately stop selling its product because the current, approved labeling would instantly become inconsistent with the pre-2016 methods of administration forced into effect by the Fifth Circuit. 21 U.S.C. § 355(a). Because mifepristone and misoprostol are GenBioPro's only products, that result threatens catastrophic financial and operational distress and puts in question GenBioPro's continued viability.

Importantly, the harm is even greater for GenBioPro than Danco because GenBioPro's reapproval 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 must wait for FDA approval of Danco's new labeling before GenBioPro can obtain approval. See *Mut. Pharm. Co.* v. *Bartlett*, 570 U.S. 472, 477 (2013).

Because the Fifth Circuit's decision requires regressing to a label with an outdated 600 mg regimen for mifepristone that was abandoned years before GenBioPro obtained approval for its generic drug, Pet. App. 10a, GenBioPro will need to redesign its entire manufacturing process to produce a three-tablet blister pack. That includes purchasing and certifying new production equipment to allow it to package doses it 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 return to the market and ability to regain its predominant stream of revenue.

Even after GenBioPro returns 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 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 and products that are already in the stream of commerce threatens confusion and turmoil for all entities that purchase, distribute, prescribe, and use mifepristone.

B. Beyond the harm to GenBioPro and its partners and affiliates, the Fifth Circuit's decision would impose immense harm on patients and health care providers across the country. The Fifth Circuit proceeded despite having been informed that, to the extent the decision eliminates access to mifepristone, even temporarily, it "may pose health risks to 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 communities facing the most obstacles to care.

There are also significant practical consequences to the specific REMS changes mandated by the Fifth Circuit. For one thing, its ruling reduces the approved period for use from ten weeks to seven—a point in time when a substantial percentage of patients do not know they are pregnant. Indeed, hundreds of thousands of

Americans each year do not confirm they are pregnant until at least 6 weeks into gestation, especially those ages 15-19, who on average do not confirm it until nearly week 7. See Amy M. Branum & Katherine A. Aherns, U.S. Ctrs. for Disease Control, *Trends in Timing of Pregnancy Awareness Among US Women*, 21 Maternal & Child Health J. 715 (April 2017), https://bit.ly/3FeuGYA. In addition, requiring three office visits would make it extremely difficult for many patients to access mifepristone, especially in certain states. And for patients who can access mifepristone, the pre-2016 labeling will 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 simply because the parties had focused predominantly on the greater harm of nullifying approval altogether. But FDA examined those harms when making its 2016 and 2021 decisions and determined the changes were appropriate. The Fifth Circuit provided no reasoned basis to depart from those conclusions, nor did it attempt to comply with Congress's express mandate that REMS programs be designed to "[a]ssur[e] access and minimiz[e] burden" on "the health care delivery system." 21 U.S.C. § 355-1(f)(2), (f)(2)(D).

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 held that this Court's stay of its decision mitigates those concerns. Pet. App. 66a-68a. But that conclusion does not follow unless this Court grants certiorari and reverses the Fifth Circuit's decision. Otherwise, this Court's stay only *delays* the harm. And because the Fifth Circuit has

required affirmative relief at the preliminary-injunction stage, all of the steps that mifepristone manufacturers, 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 petitions for writs of certiorari should be granted.

Respectfully submitted.

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