Nos. 23-235 & 23-236

In the Supreme Court of the United States

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

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents.

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

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents.

On Petitions for a Writ of Certiorari to the United States Court of Appeals for the Fifth Circuit

BRIEF FOR THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICUS CURIAE*[1]

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary nonprofit association representing the country's leading research-based pharmaceutical and biotechnology companies. PhRMA advocates in support of public policies that encourage the discovery of life-saving and life-enhancing new medicines. PhRMA's members produce innovative medicines, treatments, and vaccines that save and improve the lives of countless individuals every day. Since 2000, PhRMA's member companies have invested more than $1.2 trillion into discovering and developing new medicines, including $100.8 billion in 2022 alone. *See* PhRMA, *Annual Membership Survey* at 3 tbl. 1 (2023).[2] Although a return on these substantial investments is never guaranteed because of the risks inherent in scientific innovation and discovery, the reliability and rigor of the drug approval process facilitated by the Federal Food and Drug Administration ("FDA") makes that risk tolerable.

PhRMA's members share a significant interest in protecting against disruptions to the stable and predictable statutory framework Congress created to govern FDA's drug approvals. The framework Congress established in the Federal Food, Drug, and

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[1] In accordance with Rule 37.2, all counsel of record received timely notification of *amicus curiae*'s intent to file this brief. No party's counsel authored this brief in whole or in part. No party, counsel for a party, or person other than *amicus curiae,* its members, and its counsel made any monetary contribution intended to fund the preparation or submission of this brief.

[2] https://perma.cc/XD8B-8B8X (archived Oct. 11, 2023).

Cosmetic Act, 21 U.S.C. § 355, *et seq.* ("FDCA") is thorough and rigorous, thereby assuring patients, healthcare providers, drug and device developers, and drug and device manufacturers that the drugs approved for market by FDA are safe and effective for their intended uses. The Court should grant the petitions and reverse the Fifth Circuit's judgment because it sets a precedent that—if left undisturbed—could significantly disrupt industry and stifle innovation in drug development.

INTRODUCTION AND SUMMARY OF ARGUMENT

Congress vested FDA with unique authority when it comes to evaluating the safety and efficacy of drugs. For decades, biopharmaceutical companies, healthcare providers, patients, and other stakeholders have relied on FDA's expert judgments on drug approval, labeling, and post-approval marketing requirements. Indeed, biopharmaceutical companies invest tens of billions of dollars every year against the regulatory backdrop that Congress established.

The Fifth Circuit's ruling upends this settled regulatory scheme and the investments that hinge upon it. If left undisturbed, the court's reasoning could invite boundless litigation to FDA drug approvals. Under these specific facts, the Fifth Circuit concluded the challenge to the initial approval of the drug at issue in 2000 was likely barred by the statute of limitations. But in affirming the suspension of FDA's 2016 changes to that drug's approved conditions of use ("2016 Amendments") and 2021 elimination of the drug's in-person dispensing requirement ("2021 Non-Enforcement Decision"), the court paved a new path to contest both initial FDA drug approval and subsequent supplemental drug approvals. Should the decision below stand, FDA's safety determinations will risk becoming mere precursors to litigation, rather than durable decisions that protect a company's massive investment in the product's lengthy research and development process.

The Fifth Circuit's ruling threatens to stifle pharmaceutical innovation by disrupting industry's

reasonable investment-backed expectations. Congress created an FDA approval process that is both rigorous and thorough, and pharmaceutical companies invest billions of dollars in research and development to meet FDA's scientific standards. Considering the rigorousness of this process and the due process interests of drug sponsors, Congress also mandated by statute a process for withdrawal or suspension of an FDA approval decision—a process the Fifth Circuit circumvented. But if *every* FDA drug approval decision—and subsequent supplemental drug approval decision—can be retroactively invalidated by a court based on extra-statutory, judicially created requirements, biopharmaceutical companies will likely invest less in the advancement of new and existing medicines that benefit patients.

In short, the panel's ruling is deeply flawed and would jeopardize the settled regulatory framework on which the biopharmaceutical industry—and the patients it serves—relies. The Court should grant the petitions filed by FDA and Danco Laboratories, L.L.C., and reaffirm FDA's statutorily prescribed authority to make crucial drug safety and effectiveness determinations, including post-approval. Permitting courts to second-guess FDA's congressionally delegated science-based safety judgments could destabilize the pharmaceutical and biotechnology industry, incentivize litigation by third parties, and discourage innovation in drug development, all to the ultimate detriment of patients.

ARGUMENT

REVIEW IS MERITED BECAUSE THE FIFTH CIRCUIT'S DECISION THREATENS TO CHILL PHARMACEUTICAL INNOVATION BY DISRUPTING INDUSTRY'S INVESTMENT-BACKED EXPECTATIONS.

The biopharmaceutical industry relies on the stability of the pre- and post-approval drug evaluation process that Congress vested FDA with authority to administer. Companies make decisions to invest in the research and development of medicines, and in post-approval studies and supplemental new drug applications, with the expectation that their enormous financial investments will ultimately generate a return that can lead to the advancement of future medicines. When a company satisfies FDA's rigorous pre- and post- approval standards, that determination should not be second-guessed by courts.

If the Fifth Circuit's decision is allowed to stand, FDA's approval determinations will no longer provide the stability our system requires. The Fifth Circuit's ruling supplants FDA's role and circumvents the regular channels for withdrawal of drug approval that safeguard the due process interests of drug sponsors. In doing so, the decision threatens to disrupt the cycle of drug development and to upend the investment-backed expectations of industry that ultimately undergird the availability of innovative medicines on which patients rely.

A. Congress Directed FDA to Apply Its Expertise By Making Science-Based Safety and Effectiveness Decisions.

FDA's congressionally mandated "[m]ission" is to "protect the public health by ensuring that . . . drugs are safe and effective." 21 U.S.C. § 393(b)(2)(B). Consistent with the applicable statutory commands, this Court has emphasized that FDA's "objective" is to "ensure that any product regulated" is "'safe' and 'effective' for its intended use." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000). Indeed, that "essential purpose pervades the FDCA [Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355, *et seq.*]" *Id.*

Congress required that FDA approve a drug before it can be "introduce[d] or deliver[ed] for introduction into interstate commerce." 21 U.S.C. § 355(a), (d). FDA's initial approval of the drug must be based on a demonstration that the drug is safe and effective for its intended use. This standard—that the drug be safe and effective for its intended use—remains the standard for changes made after the initial approval. FDA's pre-approval process is lengthy and rigorous, and all major changes, including all changes based on post-marketing studies, require a similarly detailed review.

To start the approval process for a new drug, a pharmaceutical company must generally conduct a series of laboratory studies to test how a proposed medicine works and assess its safety. *See* 21 C.F.R. § 312.23(a)(8). If the results of such studies are promising, the company submits an investigational New

Drug Application to FDA that outlines those results and offers a plan for clinical trials. *See* 21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)–(b). After completing multiple rounds of clinical trials, the company can submit a New Drug Application to seek FDA drug approval. *See* 21 C.F.R. § 312.21. The New Drug Application often exceeds 100,000 pages in length and must include (among other things) "full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A).

Once a New Drug Application is filed, an FDA review team comprised of multidisciplinary experts diligently evaluates whether the studies submitted show that the drug is safe and effective for its proposed use. "Safe" in this context means that the benefits of the drug outweigh the known risks. Effectiveness must be based on "substantial evidence"—*i.e.*, "evidence consisting of adequate and well-controlled investigations." *See Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 613 (1973) (FDA must "refuse approval" of a New Drug Application "if 'substantial evidence' that the drug is effective for its intended use is lacking"). If FDA concludes that a drug is safe and effective for its proposed use and finds that "none" of seven specified "grounds for denying approval" apply, then FDA can approve the drug for use. *See* 21 U.S.C. § 355(c)(1)(A), (d).

Following that initial drug approval, companies continue to study approved products and invest in post-approval research. Post-approval investment may culminate in a supplemental application to FDA seeking changes that, among other things, extend the

drug approval to treat another disease or condition; expand the patient population that a drug is approved to treat; or approve a new dosing schedule that allows a drug to be taken less frequently. These "Supplemental New Drug Applications" are generally subject to the same procedures and actions as original New Drug Applications, *see* 21 U.S.C. § 355(b), and they similarly involve the submission of extensive supporting information.

Congress also gave FDA statutory authority over drug safety programs known as Risk Evaluation and Mitigation Strategies ("REMS"), which may be implemented as part of an original or supplemental approval. *See* 21 U.S.C. § 355-1. REMS focus on preventing and managing risks associated with use of a drug—for example, by reinforcing particular practices among providers and patients. FDA's authority over REMS includes requiring modifications to "ensure the benefits of the drug outweigh the risks of the drug," or to "minimize the burden on the health care delivery system of complying with the [REMS]." *Id.* § 355-1(g)(4)(B)(i), (ii). A drug application holder also may propose a REMS modification through a Supplemental New Drug Application based on an "adequate rationale" that supports the change. *Id.* § 355-1(g)(4).

In addition to the authority to approve drugs, evaluate subsequent changes, and administer REMS, Congress vested FDA with the exclusive authority to withdraw approval of a New Drug Application or a Supplemental New Drug Application. An approval can be withdrawn if FDA finds that "experience," "tests," "scientific data," or other "new evidence" show that the drug "is unsafe for use under the conditions"

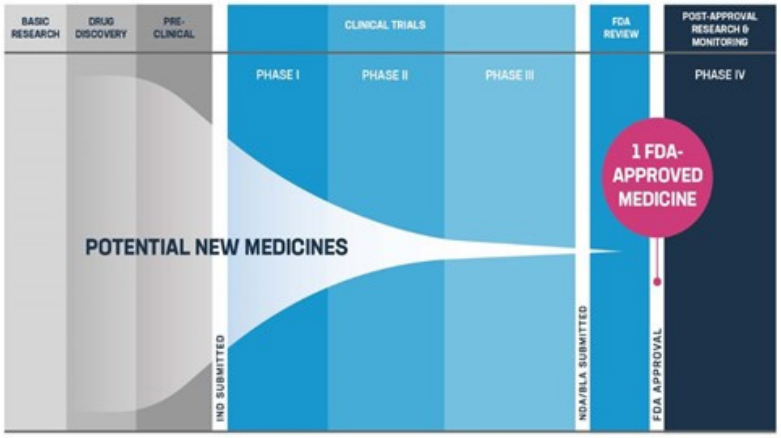
for which it was approved. 21 U.S.C. § 355(e). As part of the withdrawal, Congress required FDA to provide the holder of the drug application "due notice and opportunity for hearing" before withdrawing or suspending approval. *Id.* But, if FDA makes a series of findings that "there is an imminent hazard to the public health," it can suspend a drug approval "immediately," although it must provide the drug application holder with an opportunity for an expedited hearing after suspension. *Id.*

As many courts and jurists have recognized over the years, "[a] court is ill-equipped to second-guess" FDA's "scientific judgment" under the guise of the Administrative Procedure Act's arbitrary-and-capricious standard. *Cytori Therapeutics, Inc. v. FDA*, 715 F.3d 922, 927 (D.C. Cir. 2013) (Kavanaugh, J.). Indeed, "courts owe significant deference to the politically accountable entities with the 'background, competence, and expertise to assess public health.'" *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578, 578–79 (2021) (Roberts, C.J., concurring in grant of application for stay).

B. The Biopharmaceutical Industry Makes Enormous Investments in Research and Development in Reliance on the Stable Regulatory Scheme that FDA Administers.

Researching and developing medicines is expensive and risky for pharmaceutical companies. Compliance with FDA's review process, summarized above, requires enormous resources and effort. From drug discovery through FDA approval, developing a new medicine typically takes at least 10 years and

costs an average of $2.6 billion. *See* PhRMA, *Research & Development: Clinical Trials*.[3] Just one out of every 5,000 to 10,000 compounds under development, and less than 12% of the candidate medicines that make it into Phase 1 clinical trials, are approved by FDA as meeting its safety and effectiveness standards. *See id.* Although hundreds of thousands of compounds are initially investigated as potential drugs, and hundreds proceed to clinical trials, FDA has approved an average of only 38 drugs annually between 2010 and 2019 (which was an increase over the previous decade). *See* Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* at 1 (Apr. 2021) ("CBO Report").[4] This winnowing process is illustrated by the graphic below:



PhRMA, *Research & Development: Clinical Trials.*

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[3] https://perma.cc/EMP4-RQLY (archived Apr. 29, 2023).

[4] https://perma.cc/2NTL-PHJ2 (archived Apr. 29, 2023).

To develop new drugs, support their approval, and further explore post-approval innovations, pharmaceutical companies make extraordinary expenditures on research and development. For example, since 2000, PhRMA member companies have invested more than $1.2 trillion in the development of new treatments and cures, including $100.8 billion in 2022 alone. *See* PhRMA, *Annual Membership Survey* at 3 tbl. 1. That year, 11.5% of the total research and development expenditures were to support post-approval research and development. *See id.* The benefits of post-approval research have been particularly significant in oncology medicines. Nearly 60 percent of oncology medicines approved over a decade ago received additional approvals in later years, leading to new indications and treatments and improved patient care. PhRMA, *Cancer Post Approval Infographic* (Aug. 2022).[5]

Indeed, the biopharmaceutical sector is the most R&D-intensive industry in the Nation's economy. Over the past ten years, PhRMA's member companies have spent an average of approximately 21% to 25% of their domestic sales revenue on research and development. *See* PhRMA, *Annual Membership Survey* at 4, tbl. 2. By contrast, that same figure across all other industries "typically ranges between 2 percent and 3 percent." CBO Report at 3. Even other investment-dependent enterprises—like software and semiconductor companies—spend significantly less than biopharmaceutical companies as a proportion of sales. *See id.*

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[5] https://perma.cc/3QXZ-7U44 (archived Oct. 3, 2023).

C. The Fifth Circuit's Flawed Decision Rests on a Basic Misunderstanding of the FDCA.

The Fifth Circuit nullified FDA's actions by imposing unworkable, extra-statutory requirements and misapprehending critical features of the governing statutory framework. Although the court's analysis purports to be limited to the 2016 Amendments and the 2021 Non-Enforcement Decision, the reasoning has far-reaching implications for initial and supplemental drug approvals. *Amicus* highlights several of the court's fundamental errors and their effects.

1. Congress Did Not Require All Changes to Conditions of Use to Be Assessed in a Single Controlled Study Before Implementation.

In 2016, FDA approved a Supplemental New Drug Application to change various conditions of use for the drug at issue (*e.g.*, allowing prescriptions by licensed non-physician providers, adjusting the dosage, increasing the time under which to prescribe, and modifying the method of administration). At the time, FDA concluded that the 2016 Amendments were supported by ample scientific evidence gathered over decades of use—and in making this determination, FDA considered at least three studies that tested the same or similar changes that were then implemented in the 2016 Amendments. *See, e.g.*, C.A. Add. 782 nn.1, 3, 4 (FDA Summary Review, Mifeprex REMS Changes (Mar. 29, 2016)).[6]

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[6] "C.A. Add." refers to the addendum to FDA's motion for a stay pending appeal in the Fifth Circuit (No. 23-10362 Dkt. 27).

Nevertheless, the Fifth Circuit determined that FDA's decision to approve that Supplemental New Drug Application was invalid because FDA allegedly "did not consider the cumulative effect of the 2016 Amendments" given that "[n]one of the studies [FDA] relied on examined the effect of implementing all of those changes together." FDA Pet. App. 53a; *see also* FDA Pet. App. 235a (stay ruling) (faulting FDA for citing "zero studies that evaluated the safety-and-effectiveness consequences of the 2016 [Amendments] *as a whole*"). In other words, the Fifth Circuit effectively imposed a requirement that *all* proposed changes to a medication's conditions of use in the context of a Supplemental New Drug Application must be assessed together in a single controlled study.

That requirement was a judicial imposition. There is nothing in the governing statute that requires FDA to base changes to a drug's conditions of use on a single controlled study testing the cumulative impact of the proposed changes. *See generally* 21 U.S.C. § 355. The statute establishes rigorous standards, but the framework established by Congress requires sufficient testing for FDA to evaluate proposed conditions of use for safety and efficacy for patients' benefit without the type of study suggested by the Fifth Circuit.

As described above, Supplemental New Drug Applications generally must be approved through the same procedures and actions as original New Drug Applications. *See* 21 U.S.C. § 355(b). And through this careful process, FDA approves an average of 200 such applications every year to support new uses, provide treatment to different patient populations,

modify conditions of use, and the like. *See* FDA, *Report of Summary Level Review Under Section 3031 of 21st Century Cures* (2023).[7] The FDCA includes no requirement that FDA rely on a controlled study testing the cumulative "effect of implementing all of [the proposed] changes together," FDA Pet. App. 53a, before approving a Supplemental New Drug Application. The same is true of a REMS modification. Regardless of the grounds for a REMS modification's submission, Congress did *not* require FDA to cite a controlled study, let alone a controlled study that tests the proposed changes together. *See* 21 U.S.C. § 355-1.

The Fifth Circuit's novel, judicially imposed requirement that FDA examine the effect of *all* proposed changes through a single controlled study could cause real harm to healthcare providers, patients, and pharmaceutical innovation. Such a controlled study would be costly, lengthy, and difficult (if not impossible) to design. As a result, important changes to medicines—such as new indications, expanding the approved use of an existing drug to include new patient populations, or modifications to dosing schedules—would happen slowly or not at all. Further, various medications would be subject to REMS restrictions that would plainly be unwarranted based on current data, and yet would be frozen in place.

In short, the Fifth Circuit's requirement that an approval must be based on a single controlled study consisting of all proposed changes is impracticable (if not impossible), harmful to society, and contrary to law. This Court should review this case to clarify that

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[7] https://perma.cc/E7QB-G6HA (archived Sept. 29, 2023).

FDA must follow its governing statute—not directives unmoored from its text—when modifying a drug's conditions of use.

2. Congress Did Not Require FDA to Collect Additional Adverse Event Data to Evaluate the Safety of a Proposed REMS Modification.

The Fifth Circuit held that the 2021 Non-Enforcement Decision (which effectively removed the in-person dispensing requirement) was arbitrary and capricious in part because, in the Fifth Circuit's view, FDA "no longer had access to perhaps the best source of [adverse event] data: the prescribers." FDA Pet. App. 59a. That reasoning stemmed from a flawed understanding of the adverse event reporting data available to FDA.

Adverse event reporting responsibilities start with the holder of the drug application, which is often the drug manufacturer. Federal law *mandates* that the holder of the drug application maintain records and report information relating to clinical experience and other data the manufacturer receives or obtains to FDA as prescribed by regulation so that FDA can determine whether there may be grounds for withdrawing a drug approval under 21 U.S.C. § 355(e). 21 U.S.C. § 355(k)(1). FDA's implementing regulations in turn require reporting of *all* adverse events to FDA. *See* 21 C.F.R. §§ 314.98, 314.80, 314.81. The holder of the drug application must promptly review all adverse event information obtained directly and indirectly from any source, including healthcare providers, patients, postmarketing clinical investigations, epidemiological/

surveillance studies, scientific literature, and unpublished scientific papers, and must establish procedures for the surveillance, receipt, evaluation, and reporting of adverse events to FDA. *See id.* § 314.80(b). Once a drug application holder has received and reviewed adverse event information, it is *required* to submit reports to FDA. *Id.* § 314.80(c).

Federal law also encourages other stakeholders such as physicians and patients to voluntarily report adverse events. *See* 21 U.S.C. § 352(n) (providing that a prescription drug shall be deemed misbranded, subject to limited exceptions not applicable here, unless published direct-to-consumer advertisements contain the statement "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1–800-FDA-1088."); *see also* 21 C.F.R. § 201.57(a)(11)(ii) (requiring prescription drug product labels contain contact information for the manufacturer and FDA for reporting).[8]

Stakeholders have a strong incentive to report adverse events to the application holder to improve patient healthcare. *See, e.g.*, Gerald J. Dal Pan et al., *Postmarketing Spontaneous Pharmacovigilance Reporting Systems, in Textbook of Pharmacoepidemiology* 115, 118 (Brian L. Strom et al. eds., 3d ed. 2021). In fact, to facilitate adverse event

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[8] Healthcare providers and patients can easily report adverse events on FDA's MedWatch website. *See* https://www.accessdata.fda.gov/scripts/medwatch/index.cfm (last visited Oct. 10, 2023).

reporting, federal law generally requires that prescription drug product labeling include the following verbatim statement:

> To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at (insert current FDA phone number and Web address for voluntary reporting of adverse reactions).

21 C.F.R. § 201.57(a)(11)(ii).

FDA then collects all adverse event reports received from all sources—including drug application holders, healthcare providers, and patients—in a database, known as FAERS (short for "FDA Adverse Event Reporting System"). *See, e.g.*, FDA, *Adverse Event Reporting System*[9] (FAERS "is a database that contains information on adverse event and medication error reports submitted to FDA."). The FAERS system has long provided a source of information for FDA to monitor an approved drug's safety after it enters the market.

The 2016 Amendments removed only *one* reporting measure for the drug at issue: the *requirement* that *healthcare providers* report *non-fatal* events. Contrary to the Fifth Circuit's assumption, *see* FDA Pet. App. 59a, FDA did not lack "access" to adverse event reports from prescribers. Even after the 2016 Amendments, healthcare providers were still required to report any fatal adverse events (in the exceedingly

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[9] https://open.fda.gov/data/faers/ (last visited Oct. 10, 2023).

rare instance that such an event might occur). And the manufacturers also remained subject to mandatory reporting requirements for *all* adverse events (fatal or non-fatal) under the regulations described above. And healthcare providers and others could voluntarily submit report non-fatal adverse events to FAERS. Thus, FDA continued to receive adverse event reports from multiple sources, just as it does for every FDA-approved drug.[10]

In light of the above, it was not arbitrary or capricious for FDA to rely on a "thorough scientific review" of the "available clinical outcomes data and adverse event reports" when issuing the 2021 Non-Enforcement Decision. C.A. Add. 841, 861–72 (FDA Denial Letter, 2019 Citizen Petition (Dec. 16, 2021)). A contrary conclusion could have startling implications. Congress required drug application holders to maintain records and make reports to FDA, in accordance with the framework implemented through FDA's regulations, to facilitate the determination of whether there may be ground for withdrawal of an approval. *See* 21 U.S.C. § 355(k). Congress further mandated that FDA's recordkeeping and reporting framework have "due regard for the professional ethics of the medical profession and the interests of patients." *Id.* Consistent with these Congressional directives, FDA has instituted and implemented a framework comprised of mandatory adverse event reporting by drug application holders and voluntary reporting by providers and patients captured in the FAERS database.

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[10] This is in addition to the adverse event reports compiled during the fifteen plus years the drug was subject to mandatory reporting from physicians and the manufacturer.

Here, even after the 2016 Amendments, the adverse event reporting requirements still exceeded the reporting requirements applicable to the vast majority of other drugs on the market. If the FAERS database and other safety data evaluated by FDA were deemed "insufficient" to ground FDA's safety determinations here, FDA Pet. App. 59a–60a, it would upend the very system Congress directed FDA to implement and invite unwarranted challenges to countless other FDA-approved drugs. This Court should correct that consequential error.

D. The Decision Below Will Jeopardize Innovation and Disrupt Industry's Settled Reliance Interests.

Biopharmaceutical companies invest substantial time and resources into research and development based on the reasonable expectation—grounded in the exclusive regulatory authority Congress has conferred on FDA—that absent exigent circumstances, once a New Drug Application (or Supplemental New Drug Application) is approved by FDA, it will be lawful and potentially profitable to market that product in accordance with the conditions of that approval for an extended period anywhere in the United States.

Without that assurance, the incentive to innovate diminishes. The reason is simple. If every new or supplemental approval decision is subject to an appreciable risk of being upended by a court based on judicial assessments of studies, judicial reweighing of evidence, and judicially fashioned *post hoc* requirements, biopharmaceutical companies could have dramatically lower predictability regarding return on

investment from an approved drug and thus decide to invest less in the advancement of medicines. *See* CBO Report at 1 (explaining that investment amounts are a function of anticipated revenues).

The Fifth Circuit dismissed the substantial impact its ruling would have on the biopharmaceutical industry, confining its destabilizing effect to "apply[ing] primarily (if not wholly) to the challenge to the [original] 2000 Approval." FDA Pet. App. 68a. But left uncorrected, the Fifth Circuit's reasoning could provide the basis for challenging the initial approval of other FDA-approved drugs. Although here the Fifth Circuit concluded the challenge to the drug's initial approval was likely barred by the statute of limitations, FDA Pet. App. 3a, the statute of limitations might not pose a barrier to judicial review next time—and, if the court's reasoning stands, there will be a next time. The newfound vulnerability of initial drug approval may undermine incentives to invest and chill innovation in the pharmaceutical industry.

Even if the Fifth Circuit's decision were limited to subsequent supplemental drug approval decisions, it could still upend the substantial investment a Supplemental New Drug Application represents. Preparing and submitting a Supplemental New Drug Application is often an enormous and costly undertaking. *See* pp. 7–8, 10, *supra*. These approvals are responsible for expanding treatment options for patients, modifying conditions of use, and supporting other crucial changes. That same process is required to modify a REMS, which in turn affects how a drug is distributed to prescribers, dispensers, and patients. REMS also determines the labeling distributed with a drug.

Down the distribution chain, manufacturers rely on the certainty that FDA's REMS decisions provide in order to make consequential business decisions, like entering into contracts with third parties to implement the REMS program. Reversing or staying a REMS modification, then, is not like flipping a switch. It could require sweeping changes across the REMS implementation scheme, resulting in delays and supply chain breakdowns, with serious downstream impacts on patient care.

And even setting aside the impact on FDA approval, the Fifth Circuit's ruling contravenes the congressionally prescribed process for withdrawing or suspending such approval. Understanding the gravity of withdrawal or suspension of an FDA approval, Congress established in the FDCA a process by which FDA can withdraw approval of a New Drug Application or a Supplemental New Drug Application. *See* pp. 8–9, *supra*. By staying an approval outside of that established framework, the Fifth Circuit disregarded the drug application holder's settled reliance interests in the preexisting drug approval. That approach is not only inconsistent with the process Congress provided, but also represents a destabilizing threat to the investment-backed expectations that make drug innovation possible.

CONCLUSION

The petitions for a writ of certiorari should be granted.

Respectfully submitted,

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