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.*,
Respondents.

DANCO LABORATORIES, L.L.C.,
Petitioner,
v.
ALLIANCE FOR HIPPOCRATIC MEDICINE, *et al.*,
Respondents.

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

BRIEF OF PHARMACEUTICAL COMPANIES, EXECUTIVES, AND INVESTORS AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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October 12, 2023

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STATEMENT OF INTEREST[1]

Amici curiae are pharmaceutical companies and executives and pharmaceutical-industry associations and investors from across the United States. A full list of *amici* is included as an Appendix to this brief.

The Fifth Circuit's decision in this case radically alters the new drug application ("NDA") process through which drug sponsors seek and maintain Food and Drug Administration approval of new pharmaceutical products for sale and marketing. *Amici* collectively hold hundreds of approved NDAs and anticipate filing many more for drugs currently in development. They are deeply familiar with the high costs associated with drug development and the need for regulatory clarity, certainty, and stability around drug approval and post-approval changes. As a result, they are well positioned to explain to this Court how the decision below will upend these processes and chill drug development.

INTRODUCTION AND SUMMARY OF ARGUMENT

Each year, pharmaceutical developers and investors devote billions of research-and-development dollars to creating new medications that improve health and save lives. In the United States, the process by which those medications are evaluated to ensure that they are safe and effective is the product

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[1] No counsel for any party authored this brief in whole or in part, and no person other than *amici*, their members, and their counsel made a monetary contribution to the preparation or submission of this brief. Counsel of record for all parties received timely notice of *amici*'s intent to file this brief.

of nearly a century of federal legislation delegating oversight of drug approvals to the Food and Drug Administration ("FDA"). This process does not end when a drug is approved. Rather, drug developers continuously monitor and make improvements to their products.

The decision below, which cast aside FDA's expert determination that mifepristone is safe and effective under its approved conditions of use, upended that longstanding statutory and regulatory framework. In response to a claim by an organization whose members do not use or prescribe the drug at issue, the court of appeals disregarded settled principles of arbitrary-and-capricious review and improperly second-guessed FDA's sound and reasonable scientific decisions. For instance, it substituted the court's non-expert judgment for FDA's rigorous, data-driven scientific analysis; erroneously concluded that FDA must ordinarily require a study that mirrors the specific combination of conditions under which a drug will be used; and dismissed as unreliable the adverse-event reporting system that FDA uses for nearly all approved drugs.[2]

That decision, if allowed to stand without further review, would sharply and unnecessarily restrict the availability of a drug that has been FDA-approved for nearly a quarter-century. But that is not all. Far from being limited to a single drug, the logic of the decision below will create chaos for the drug development and

[2] This brief focuses on the Fifth Circuit's holdings that pose the greatest threat to drug development; it does not address all of the lower courts' erroneous holdings in this case.

approval processes. That decision casts a shadow of uncertainty over every FDA approval and invites spurious lawsuits challenging FDA's safety and effectiveness determinations. Under the Fifth Circuit's logic, any physician, whether or not they actually treat patients using the drug in question, can ask a judge to undermine patient access to any drug nationwide, based on nothing but disagreement with FDA's scientific judgment. The destabilizing effects of that outcome cannot be overstated. It would chill crucial research and drug development, undermine the viability of investments in this important sector, and wreak havoc on drug development and approval generally—irreparably harming patients, providers, and the entire pharmaceutical industry.

This is not a case where review can wait. As is evident from the lengthy list of *amici* joining this brief, the decision below has raised serious concerns for the entire pharmaceutical industry. If certiorari were denied and this Court's stay were allowed to expire, the consequences of that decision would extend far beyond this particular drug and the patients and providers that depend on it. *Amici* urge this Court to grant certiorari and reverse the judgment below.

BACKGROUND

A. Congress intended FDA, not the courts, to serve as the expert arbiter of drug safety and effectiveness.

Since its enactment nearly a century ago, the Federal Food, Drug, and Cosmetic Act ("FDCA") has required that FDA determine that a new drug is safe before it can be marketed. Pub. L. No. 75-717, 52 Stat.

1040 (1938) (codified as amended at 21 U.S.C. § 301 *et seq.*). In the 1960s, Congress added a requirement that FDA determine that a drug is also effective. Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781–82 (codified as amended at various sections of 21 U.S.C.). These requirements of safety and efficacy are the touchstones of FDA review.

Over the last sixty years, Congress has repeatedly expanded FDA's authority and affirmed FDA's role as the arbiter of whether and under what conditions of use a drug should be made publicly available. *See, e.g.*, Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823; Food and Drug Administration Safety and Innovation Act of 2012, Pub. L. No. 112-144, 126 Stat. 993. FDA has faithfully implemented those requirements and promulgated regulations setting forth the scientific principles governing adequate and well-controlled clinical investigations and the requirements for labeling of approved drugs. *See, e.g.*, 21 C.F.R. §§ 201.56, 201.57, 314.50, 314.126. With those statutory and regulatory guardrails in place, FDA has retained significant flexibility in the drug-approval process—flexibility that is essential to allow the agency to apply its expert scientific and medical judgment on a case-by-case basis and to maximize opportunities for drug development, continuous improvement, and patient access to innovative medicines that match the latest scientific evidence.

B. Drug sponsors must demonstrate safety and effectiveness before FDA approval.

The NDA process. Under the FDCA framework, FDA will approve an NDA only if the application

includes sufficient evidence of safety and "substantial evidence" of effectiveness from "adequate and well-controlled investigations." 21 U.S.C. § 355(d); *see id.* §§ 321(p), 331(d), 355(a). To meet this standard, the drug sponsor typically undertakes a lengthy and resource-intensive development program. As part of that program, the sponsor performs rigorous scientific studies and analyses, including: laboratory testing; preclinical (animal) testing; three separate phases of clinical studies involving, on average, several thousand patients; developing chemistry, manufacturing, and controls information; and developing label information to direct physician prescribing. Scientific and medical experts at FDA engage with the drug sponsor throughout the process, which culminates when the sponsor submits, and FDA reviews, the NDA.

FDA's decision to approve an NDA is predicated on a rigorous analysis performed by physicians and other scientific experts within the agency. At the end of that process, FDA will approve the NDA only if it concludes that the drug is safe and effective under the conditions prescribed, recommended, or suggested in the proposed labeling. 21 U.S.C. § 355(b)–(d); 21 C.F.R. § 314.50(a)(1).

The sponsor of an approved NDA must notify FDA of each change it wishes to make to the approved conditions in the NDA, including changes to labeling. With minimal exceptions, this is done through submission of a supplemental NDA ("sNDA"). *See* 21 C.F.R. § 314.70(b); *Wyeth v. Levine*, 555 U.S. 555, 568 (2009) ("Generally speaking, a manufacturer may only change a drug label after the FDA approves a

supplemental application."); FDA, Guidance for Industry: Changes to an Approved NDA or ANDA at 4 (rev. 1, Apr. 2004). FDA reviews sNDAs under the same standards that govern its review of original applications, meaning it will approve an sNDA only if it determines that the drug will be safe and effective under the changed conditions of use proposed in the sNDA. *See* 21 C.F.R. § 314.3 (defining "application" to include "amendments and supplements"); *id.* §§ 314.70, 314.125.

These statutorily mandated determinations of safety and effectiveness turn on FDA's assessment of the drug's benefit-risk profile. Because all drugs have the potential for adverse effects, demonstrating a drug's safety does not require the sponsor to show that the drug has *no* potential adverse effects, but rather that the drug's benefits outweigh any risks it poses. *See* 21 U.S.C. § 355(d) ("The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks …."); FDA, Draft Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products at 3 (Sept. 2021) ("Because all drugs can have adverse effects, the demonstration of safety requires a showing that the benefits of the drug outweigh its risks."); *see also Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013) ("In order for the FDA to consider a drug safe, the drug's probable therapeutic benefits must outweigh its risk of harm." (quotation marks omitted)). This balancing of benefits and risks is the core of FDA's drug-approval standard—whether FDA is considering a new original

application or an sNDA. It was entrusted by Congress to FDA as the expert agency, not to the courts.

Adverse-event reporting. All known adverse drug experiences must be reported to FDA, with only a handful of narrow exceptions not applicable here. 21 C.F.R. § 314.80. FDA regulations require that all NDA holders must review adverse drug experience information received from any source and report fatal *and* non-fatal adverse events to the agency; the only question is when, not whether, these events must be reported. First, NDA holders must report all "serious and unexpected" adverse drug experiences within fifteen days. *Id.* § 314.80(c)(1)(i). Unless already identified in the drug's labeling (and thus not "unexpected"), this includes deaths, life-threatening conditions, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, as well as other medical events that, based on appropriate medical judgment, may endanger the patient or may require medical or surgical intervention to prevent a dangerous outcome. *Id.* § 314.80(a). Second, NDA holders also must report all other adverse events on a periodic basis even though they fall outside of the regulatory definition of "serious and unexpected." *Id.* § 314.80(c)(2) (requiring quarterly reporting for the first three years post-approval and annual reporting thereafter). FDA has determined that this reporting paradigm is an appropriate means of identifying "potential serious safety problems with marketed drugs" and has relied on it for almost 40 years. FDA, New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7471 (Feb. 22, 1985).

Congress has authorized FDA to require yet additional adverse-event reporting—for example, by requiring physicians to report certain types of adverse events—only if FDA determines that such measures are necessary to assure safe use of the drug. *See* 21 U.S.C. § 355-1(f)(3). Congress also required that, when FDA does so, the agency must periodically reassess whether such requirements continue to be necessary, based on its expert judgment and analysis of input received from patients, physicians, pharmacists, and other healthcare providers. *Id.* § 355-1(f)(5). If not, FDA must pare back those requirements to "minimize the burden on the health care delivery system." *Id.* § 355-1(g)(4)(B).

For all approved drugs, FDA collects reports of adverse events experienced by patients in its Adverse Event Reporting System ("FAERS"). This comprehensive database includes information from NDA holders as well as voluntary reports from healthcare professionals and consumers. FDA routinely relies on FAERS data to support its postmarketing safety surveillance efforts.

C. FDA's drug-approval process is the gold standard of scientific review.

FDA's drug-review process is recognized worldwide as the gold standard for assuring patients that the drugs they take are safe and effective. The imprimatur of FDA approval thus has been and remains critical to uptake and acceptance of new drugs, especially for cutting-edge technologies. Accordingly, clarity and predictability are particularly important in the context of drug development, which presents considerable expense and business risk.

Only a small fraction of research-and-development programs reach the point of FDA approval, and the cost of developing a single new drug can exceed two billion dollars. *See* Cong. Budget Office, No. 57025, Research and Development in the Pharmaceutical Industry at 2 (Apr. 2021). Companies that invest in developing potentially lifesaving drugs must be able to rely on courts to respect FDA's expert scientific judgments. If a court can overturn those judgments many years later through a process devoid of scientific rigor, the resulting uncertainty will create intolerable risks and undermine the incentives for such investment. This, in turn, will ultimately hurt patients.

ARGUMENT

The decision below is highly disruptive to settled understandings of the drug-approval process. The Fifth Circuit held that FDA's approval of various changes to mifepristone's conditions of use would likely be found to be arbitrary and capricious in violation of the Administrative Procedure Act. In so holding, the court substituted its own idiosyncratic views for the gold-standard benefit-risk analysis required by Congress and performed by FDA's medical and scientific professionals. Instead of appropriately deferring to FDA's scientific expertise, and in lieu of using the approval standards established by Congress and implemented by FDA, the court invented its own novel and unworkable standards to govern drug development and approval.

If allowed to stand, the decision below will invite a flood of meritless challenges to FDA's drug-approval decisions brought by parties with no concrete interest

at stake. Drugs on which patients have depended for years could, with little warning, have their FDA-approval status undermined or be forced to dramatically alter their conditions of use. The resulting instability, litigation, and patchwork of judicial decisions will inject an intolerable level of uncertainty into the drug approval process, undercutting drug development and investment and chilling innovation.[3]

I. The Fifth Circuit improperly substituted its own views for FDA's expert scientific judgment.

The decision below represents a radical departure from the deference courts conducting arbitrary-and-capricious review normally and properly afford to FDA's scientific and medical judgment. Congress intended that the nuanced benefit-risk judgments necessary for the drug-approval process would be made by the politically accountable expert agency, not by judges "without chemical or medical background." *Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 654 (1973) (quotation marks omitted); *see FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578, 579 (2021) (Roberts, C.J., concurring) ("[C]ourts owe

[3] It is notable that the district court, relying on the same flawed approach as the Fifth Circuit, went even further and stayed FDA's original approval of mifepristone in an attempt to force a drug with a 25-year record of safe and effective use to exit the market altogether. While the Fifth Circuit majority vacated that part of the district court's decision (over one judge's dissent), it did so on statute-of-limitations grounds, not because it disagreed with the court's arrogation to itself of the power to second-guess FDA's safety and efficacy determinations.

significant deference to the politically accountable entities with the background, competence, and expertise to assess public health." (quotation marks omitted)); *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976) (en banc) (court reviews agency's scientific judgments "not as the chemist, biologist or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality").

The Fifth Circuit dispensed with FDA's approvability analysis without a hint of deference to the agency's scientific expertise. As discussed in more detail below, the court quibbled with the parameters of the clinical studies on which FDA relied to make its safety and effectiveness determinations, questioned the conclusions FDA drew from its analysis of the data, and cast doubt on the validity of data from the well-established system for monitoring drug-related adverse events for all approved drugs.

The Fifth Circuit's approach conflicts with the FDCA and the APA and violates bedrock principles of arbitrary-and-capricious review. A court applying arbitrary-and-capricious review "is not to substitute 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); *see Am. Radio Relay League, Inc. v. FCC*, 524 F.3d 227, 248 (D.C. Cir. 2008) (Kavanaugh, J., concurring in part) (explaining that arbitrary-and-capricious review is not a license for courts to second-guess "highly technical determination[s] committed to [an agency's] expertise and policy discretion"). Yet the Fifth Circuit (and the district court before it) did just

that. Left unchecked, this non-expert, judicial second-guessing of FDA's scientific judgment threatens turmoil for the industry, those that invest in it, and most importantly, the patients who depend on it.

II. The decision below creates an impossibly rigid new standard for drug approval.

The Fifth Circuit's decision would create novel and inflexible requirements that would unsettle the drug-approval process and threaten to block safe and efficacious drugs from getting to market. One hallmark of the drug-approval process is its flexibility: Drug sponsors can leverage studies from many different sources, and those studies can reflect a wide range of designs, because an application need only contain sufficient data to demonstrate safety and effectiveness. 21 U.S.C. § 355; 21 C.F.R. § 314.50. Neither Congress nor FDA has imposed artificial or unnecessary limits on what form that data must take, how it must be generated, or by what formula FDA must conduct its analysis. Quite the contrary, these are fact- and program-specific issues for which FDA must be able to exercise flexibility—not least because not all disease states or treatments lend themselves to particular study designs.

A. The decision below improperly imposes a rigid trial-design requirement not found in any statute or regulation.

The Fifth Circuit held that FDA's 2016 decision to approve an sNDA modifying mifepristone's conditions of use was arbitrary and capricious because FDA supposedly failed "to address the cumulative effect" of the proposed changes and consider their "effects as a

whole." Pet. App. 53a–54a.[4] That conclusion grossly misunderstands the FDA approval process, which *always* considers the effect of the conditions under which a drug will be used, as well as any changes to those conditions. Whenever FDA approves an application (whether an original NDA or an sNDA), it determines that the drug is safe and effective for use under *all* the "conditions prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. § 355(d); *see* 21 C.F.R. §§ 314.3, 314.125.

Without citing any evidence, the Fifth Circuit suggested that the changes proposed in the 2016 supplement might be individually safe but *collectively* unsafe. It therefore faulted FDA for "stud[ying] the amendments individually," "fail[ing] to seek data on the cumulative effect," and relying on studies "none of [which] examined the effect of implementing all of those changes together" (even though the court acknowledged that some of the studies FDA relied on "considered 'multiple changes'"). Pet. App. 53a (quoting FDA, Summary Review of 2016 Amendments at 5 (Mar. 29, 2016)). The inescapable implication is that absent some special justification, FDA ordinarily must require a study that perfectly mirrors the specific combination of conditions under which a drug will be used.

That requirement is unprecedented and has no legal basis. FDA has discretion to evaluate the safety and effectiveness of a drug under its proposed

[4] "Pet. App." refers to the petition appendix in No. 23-235.

conditions of use (and any proposed changes to those conditions) using its expert scientific judgment.

To be sure, the court below tried to deny that it was imposing such a requirement. It paid lip service to the well-established principle that FDA has discretion "in determining whether a study is adequate and well controlled," Pet. App. 54a (quotation marks omitted), but then went on to suggest that FDA must require drug sponsors to either submit clinical studies that evaluate all of the proposed conditions of use in combination or provide some special reason for dispensing with that requirement—a requirement not found in any statute or regulation. It also said the problem was "not that FDA failed to conduct a clinical trial that included each of the proposed changes," but that "FDA failed to address the cumulative effect at all." Pet. App. 54a. By law, however, FDA *always* considers the combined effect of the conditions under which a drug will be used, and it undoubtedly did so here. If the Fifth Circuit meant only that FDA needed to say in so many words that it had done so, that would be an impermissible "magic words" requirement. *See Garland v. Ming Dai*, 141 S. Ct. 1669, 1679 (2021) (so long as "'the agency's path may reasonably be discerned,'" it "need not use any particular words" (quoting *Bowman Transp., Inc. v. Arkansas-Best Freight Sys., Inc.*, 419 U.S. 281, 286 (1974))). Such flyspecking is hardly a sufficient basis for disrupting millions of patients' access to a safe and effective drug.

It seems clear that the Fifth Circuit had something far more demanding in mind. For one thing, immediately after denying that it was requiring

a single study that includes all of the conditions at issue, the court approvingly quoted the district court's statement that FDA had acted arbitrarily and capriciously because it "relied on zero studies that evaluated the safety-and-effectiveness consequences of the 2016 [changes] *as a whole*." Pet. App. 54a (quotation marks omitted). And any suggestion that the decision below would not dictate the contours of clinical studies is further belied by the Fifth Circuit's conclusion that the record—which demonstrated that FDA had carefully considered numerous clinical studies, several of which "considered 'multiple changes,'" Pet. App. 53a—did not even "tend to show that FDA would have arrived at the same decision if it had considered" the changes' "cumulative effects." Pet. App. 72a.

By imposing this novel requirement, the Fifth Circuit recast deferential arbitrary-and-capricious review as an opportunity to "substitute its judgment" for that of the expert agency and rewrite the FDCA's drug-approval paradigm. *State Farm*, 463 U.S. at 43. And its decision demonstrates a deep misunderstanding of how clinical trial procedure and FDA review actually work. There are virtually always differences between clinical trial conditions and approved labeling, and FDA is not—and should not be—held to a heightened standard requiring it to justify every such difference.

Clinical trials are not intended to perfectly mirror real-world use conditions. Rather, traditional clinical trials are, and always have been, "largely separate from routine clinical practice" precisely because they are "designed to control variability and maximize data

quality." FDA, Framework for FDA's Real-World Evidence Program at 5 (Dec. 2018). For example, clinical trials, including those conducted to support post-approval changes, often have restrictive eligibility criteria and additional monitoring procedures beyond those that would (or should) apply in practice. *See* FDA, Good Review Practice: Clinical Review of Investigational New Drug Applications (Dec. 2013). These selection criteria are not required or expected to carry over into the approved labeling, nor should they preclude FDA from relying on data in support of drug approvals. The Fifth Circuit's approach disregards these longstanding practices.

The Fifth Circuit's decision would likewise hinder reliance on new data and information to support post-approval changes unless the sponsor conducts a costly, time-consuming clinical trial the conditions of which perfectly match the changes. This approach would freeze a drug in time, discourage sponsors from continuing to innovate on their existing products, and deprive patients of access to improved treatments. It would also make it more difficult for FDA to do away with onerous restrictions that real-world experience has demonstrated unnecessarily impede patient access. And it would be particularly catastrophic for drugs intended to treat rare diseases and conditions, for which clinical trials necessarily are constrained by patient numbers and important ethical considerations, as well as drugs utilizing cutting-edge technologies that rely on early clinical trials with conditions that inevitably will significantly differ from anticipated clinical practice.

The inability to nimbly update labeling would also be especially pernicious in therapeutic areas where disease states evolve quickly, requiring drug sponsors and FDA to constantly monitor and update NDAs. For example, such updates may be necessary to reflect fast-moving evidence in the context of virus mutations and developing antimicrobial resistance. The Fifth Circuit's rigid requirements would undermine FDA's ability to make these critical updates, and patients could be left with decades-old tools in fights against modern diseases. In short, the Fifth Circuit's approach could render drug development exponentially more burdensome and freeze approved conditions of use in time, depriving patients of the benefits of evolving science and imposing outdated, unnecessary burdens on industry.

B. The decision below undermines FDA's ability to rely on its adverse event reporting system for all drugs.

The Fifth Circuit faulted FDA's reliance on data from FAERS—the database where FDA compiles reports of adverse events experienced by patients while using an approved drug—to support its decision to pare back certain restrictions on distribution of mifepristone. *See* Pet. App. 59a. The court did not find that FDA violated any specific statutory or regulatory requirement, only that its actions were (in the court's view) likely to be found to be arbitrary and capricious. The Fifth Circuit's reasoning is not limited to FDA's reliance on FAERS data in this specific instance; rather, it calls into question whether FDA can ever rely on the FAERS system, again casting a

pall of uncertainty over drug development and post-approval changes.

The Fifth Circuit's caricatured description of an agency that "eliminate[s] a reporting requirement for a thing and then use[s] the resulting absence of data to support its decision," Pet. App. 59a (quotation marks omitted), bears little resemblance to reality. What really happened is that after *fifteen years* of unusually intensive monitoring of a drug that FDA had already determined to be safe, FDA pared back some of the *heightened* reporting requirements—as it was required to do, *see* 21 U.S.C. § 355-1(f), (g)—to bring them in line with the reporting requirements that apply to nearly every other approved drug. *See* FDA, New Drug Application No. 020687/S-020, REMS Modification Review at 10 (Mar. 29, 2016) (explaining that the information previously required under the REMS "is being submitted to the Agency through other pathways including spontaneous adverse event reporting and the annual report"); 21 C.F.R. § 314.80(c) (requiring sponsor to report "serious and unexpected" adverse events within 15 days and other adverse events periodically).

There is no legal basis for the Fifth Circuit's suggestion that this action was unreasonable or that it rendered the post-2016 FAERS data unreliable or unusable. Although the court was dismissive of FDA's normal adverse-event reporting requirements, in fact, those requirements are extensive and allow FDA to capture a comprehensive set of postmarketing data. A drug's sponsor must "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA." 21

C.F.R. § 314.80(b). And it must review "*all* adverse drug experience information" received from "*any* source." *Id.* (emphasis added). This includes not only reports the sponsor receives from doctors and patients, but also "information derived from commercial marketing experience," "reports in the scientific literature," and even "unpublished scientific papers." *Id.* In addition, voluntary reports are routinely submitted directly to FDA by patients and healthcare providers.

It bears emphasis that these extensive reporting requirements are the same that apply to nearly every approved drug. So the Fifth Circuit's pronouncements that this reporting regime is incapable of generating "probative data" and that the FAERS database is categorically "insufficient to draw general conclusions about adverse events," Pet. App. 59a, would cast doubt on innumerable FDA decisions beyond just those at issue here. If the Fifth Circuit's objections to these reporting requirements are correct, they would apply for all drugs. FDA would open itself up to litigation every time it relied on FAERS data to approve a change to a drug, and drug sponsors would be deprived of the certainty and predictability of a stable system for post-approval adverse event reporting.

The decision below implies that FDA must impose unnecessary and overinclusive prescriber reporting requirements in order to support any future decisionmaking that would ease restrictions on a drug. Not only would such a requirement contravene Congress's mandate that FDA pare back requirements that it determines are unnecessary and unduly burdensome, *see* 21 U.S.C. § 355-1(f)(5), (g)(4), it also

would impose another unnecessary barrier to updating approved drugs to keep pace with science.[5]

III. The Fifth Circuit's transformation of FDCA requirements will chill drug development and investment and harm patients.

In all the ways discussed above and more, regulatory flexibility and respect for FDA's scientific judgment are crucial to fostering an environment in which innovative new drugs can be developed and existing ones improved. FDA has exercised this critical flexibility in approving thousands of drugs, including numerous transformative medicines, and in updating those approvals as science evolves. Had those drugs been developed or reviewed by FDA under the Fifth Circuit's approach, it is likely that few, if any, would have been approved and avoided legal challenges to their approvals. Those that did would have their original conditions of use effectively locked in place, depriving patients of the benefits of incremental improvements such as lower doses and more convenient delivery mechanisms.

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[5] The Fifth Circuit also took issue with FDA's giving some weight to published literature that was "not inconsistent with" its conclusion that patient safety did not require in-person dispensing. Pet. App. 62a (quotation marks omitted). However, the FDCA expressly contemplates leveraging published literature to support approval decisions, whether as confirmatory or as probative in a particular way. *See* 21 U.S.C. § 355(b)(2). Once again, the Fifth Circuit's decision would create new requirements that are entirely divorced from any statutory language, and that run counter to the statute's flexibility, to dictate, after the fact, the types of data and information on which FDA can rely.

As explained, the Fifth Circuit's unworkable standards would require drug developers to conduct trials using *only* the conditions of use for which inclusion in labeling would be appropriate, or else run the risk that a court might reverse FDA's approval many years later based on a challenge brought by any doctor who disagrees with FDA's judgment. This untenable approach would ossify labeling—excluding new information gathered from outside the original clinical trials, inhibiting reliance on FAERS, and threatening further innovations. In these ways and others, the decision below threatens to shatter FDA's gold standard of scientific safety and efficacy review.

Drug development is an increasingly high-risk and high-cost endeavor, with only a small fraction of drug candidates progressing from preclinical studies through clinical trials to market. The stability of FDA's regulatory framework provides much-needed assurance to investors who fund the development of drugs. This is particularly important in early development, when drug developers must secure sufficient capital to fund expensive clinical trials. The Fifth Circuit's improper second-guessing of FDA's scientific judgment, and its imposition of new and unwarranted restrictions on the agency's decisionmaking processes, threatens to destabilize countless FDA approval decisions. This additional uncertainty would make the already high degree of risk in these investments intolerable. And without necessary investment, drug development would freeze, stifling innovation and limiting treatment options for patients.

In short, absent review by this Court, the Fifth Circuit's decision threatens a seismic shift in the clinical development and drug approval processes—erecting unnecessary and unscientific barriers to the approval of lifesaving medicines, chilling drug development and investment, threatening patient access, and destabilizing FDA's rigorous, well-established, and longstanding drug approval process, which is rooted in science and law.

CONCLUSION

For the reasons set forth above, this Court should grant the petitions for certiorari.

Respectfully submitted,

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Amanda Banks, MD, Advisor, Board Member, Cofounder and Former CEO, Blackfynn

Julia Owens, CEO, Ananke Therapeutics

Shehnaaz Suliman, CEO, ReCode Therapeutics

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Ram Aiyar, Biotech Executive

Srinivas Akkaraju, MD, PhD, Managing General Partner, Samsara BioCapital

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Elizabeth Bailey, Managing Director, RH Capital

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Chris Bond, CSO, Notch Therapeutics

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Compass Pathways plc

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