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 Writs 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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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 applicants (or "sponsors") seek and maintain Food and Drug Administration approval of pharmaceutical products for sale and marketing, destabilizing the drug development and investment landscape and depriving patients of the benefits of scientific advancement. *Amici* collectively hold hundreds of approved NDAs and anticipate filing many more for drugs currently in development, as well as innumerable supplements effectuating changes to those approved NDAs. They are deeply familiar with the high costs associated with drug development and improvement and the need for clarity, certainty, and stability in the regulatory framework governing drug approval and post-approval changes. As a result, they are well positioned to explain to this Court how, if allowed to stand, the decision below will upend these processes, chill drug development, and preclude post-approval improvements, effectively freezing drugs in time.

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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.

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. Then still more resources are devoted, after a drug is approved, to post-approval monitoring and implementation of improvements to approved drugs. In the United States, the process of evaluating those medications and changes made to them—and thus ensuring that they are (and remain) safe and effective—is the product of nearly a century of federal legislation delegating oversight of drug approvals to FDA.

The court below cast aside FDA's expert determinations that mifepristone is safe and effective under its approved conditions of use—including as those conditions have changed to account for new scientific evidence and understanding. Instead, in response to a claim by an organization none of whose members 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. It substituted the court's non-expert judgment for FDA's rigorous, data-driven scientific analysis; it erroneously concluded that FDA must ordinarily require a study that mirrors the specific combination of conditions under which a drug will be used; and it dismissed as unreliable the adverse event reporting

system that FDA uses for nearly all approved drugs.[2] In so doing, the court of appeals upended the longstanding statutory and regulatory drug approval framework.

If not reversed, that decision will 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 in the processes for drug development, approval, and modification. That decision casts a shadow of lasting uncertainty over every FDA approval and invites spurious lawsuits challenging FDA's settled safety and effectiveness determinations after the fact. Under the Fifth Circuit's logic, *any* physician can ask a judge to undermine patient access to *any* drug nationwide—even if the physician does not treat patients using that drug—based on mere disagreement with FDA's scientific judgment. The destabilizing effects of that outcome cannot be overstated. It could 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.

The Fifth Circuit's decision must be reversed. As is evident from the lengthy list of *amici* joining this brief, the decision below has alarmed the entire pharmaceutical industry—and with good reason. If

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[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.

the Fifth Circuit's decision is allowed to stand, the consequences will extend far beyond this particular drug and the patients and providers that depend on it. *Amici* urge this Court to reverse the judgment below.

BACKGROUND

A. FDA's approval process is the gold standard of scientific review.

FDA's drug-approval process, which applies to both NDAs and modifications to approved applications, 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 and drug modifications, especially those driven by adoption of new, cutting-edge technologies. Accordingly, clarity and consistency in regulatory standards 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

investment regardless of the drug at issue. This, in turn, will ultimately hurt patients.

B. 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, which apply to NDAs and post-approval modifications, 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 generally applicable regulations setting forth the scientific principles governing adequate and well-controlled clinical investigations and the requirements for labeling approved drugs. *See, e.g.*, 21 C.F.R. §§ 201.56, 201.57, 314.50, 314.126. Within these statutory and regulatory guardrails, FDA applies its expert scientific and medical judgment to

assess drugs' benefit-risk profiles on a case-by-case basis, while maximizing efficiencies in the development and continuous modernization and improvement of, and patient access to, innovative medicines that match the latest scientific evidence.

C. Drug sponsors must demonstrate safety and effectiveness before FDA approval, including both initial approval and approval of subsequent changes.

The NDA and sNDA processes. 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 that includes laboratory and extensive preclinical testing, followed by multiple phases of clinical studies (averaging several thousand patients). In addition, drug developers generate draft labeling that, once reviewed and approved by FDA, informs 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 multiple review divisions, which include physicians and other scientific experts within the agency. FDA will approve the NDA only if it concludes that the drug is safe and effective under the conditions of use in the proposed labeling. 21 U.S.C. § 355(b)–(d); 21 C.F.R.

§ 314.50(a)(1). What those conditions should be, and the specific data needed to meet the approval standard in a particular case, are matters for the Agency's expert judgment.

The drug developer's obligation does not stop at initial approval. The holder 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 not relevant here, the NDA holder proposes changes by submitting 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: It will approve an sNDA—just like an NDA—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. An sNDA must include data and information sufficient to meet the approval standard, but, as with original approvals, FDA uses its expert scientific judgment to determine the specific data package necessary to evaluate the impact on safety and efficacy of any changes and to ensure a continued positive benefit-risk assessment for the drug.

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, Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products at 3 (Oct. 2023) ("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. Congress entrusted this determination 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 every NDA holder must review adverse drug experience information received from any source. The NDA holder must report any known adverse event—whether fatal or non-fatal—to the agency. There is no question *whether* these events must be reported; the only question is *when*. NDA holders must report within fifteen days any adverse drug experience that is "serious and unexpected." *Id.* § 314.80(c)(1)(i). Unless already identified in the drug's labeling (and

thus not "unexpected"), this includes any death, life-threatening condition, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or congenital anomaly or birth defect, as well as other medical events that, based on appropriate medical judgment, may endanger the patient or require medical or surgical intervention to prevent a dangerous outcome. *Id.* § 314.80(a). 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 system 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).

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 pursuant to their extensive reporting obligations—including reports the NDA holders receive from doctors and patients and information from commercial marketing experience and scientific literature—as well as voluntary reports from healthcare professionals and consumers submitted directly to FDA. FDA routinely relies on FAERS data to support its efforts to monitor the safety of drugs after they are approved. *See, e.g.*, FDA, Best Practices for FDA Staff in the Postmarketing Safety Surveillance of Human Drug and Biological Products

§ 3 (Jan. 2024), *available at* https://www.regulations.gov/document/FDA-2019-N-3768-0014.

In addition to these adverse event reporting requirements that apply to all approved drugs, Congress has authorized FDA to require additional adverse event reporting in the rare instance when FDA determines that such measures are necessary to assure safe use of the drug—for example, by requiring physicians to report certain types of adverse events. *See* 21 U.S.C. § 355-1(f)(3). Congress also required that, when FDA imposes those additional reporting requirements, the agency must periodically reassess whether such requirements continue to be necessary, based on its expert judgment and analysis of input 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).

ARGUMENT

The decision below is highly disruptive to settled understandings of the drug-approval process. In what appears to be the first time any court has abrogated FDA's approval of a drug application (in this case a supplement) or limited the circumstances under which a drug is available based on its disagreement with FDA's judgment about safety or effectiveness, the Fifth Circuit held that FDA's approval of changes to the conditions of use for mifepristone would likely be found to be arbitrary and capricious in violation of the Administrative Procedure Act ("APA"). In so holding, the court substituted its own idiosyncratic views for the gold-standard science-based benefit-risk analysis

required by Congress and performed by FDA's medical and scientific professionals. Instead of relying on FDA's scientific expertise, and in lieu of following the approval standards established by Congress and implemented by FDA, the court invented its own novel standards for drug development and approval—standards that are wholly unworkable and would deprive industry of the critical stability that comes with FDA approval, including the FDA process for approval of labeling changes.

If allowed to stand, the decision below will invite a flood of meritless challenges to FDA's drug safety and efficacy decisions, including those brought by parties with no concrete interest at stake. The holders of NDAs for drugs on which patients have depended for years could, with little warning, have their drugs' FDA-approval status undermined or be forced to dramatically alter those drugs' conditions of use based on non-scientific judicial decision-making. Their labels could be essentially fixed in time, unable to be updated to keep pace with science in the face of overly rigid and infeasible requirements for making changes. The resulting litigation and regulatory uncertainty could destabilize the drug-approval process, undercut drug development and investment, chill innovation, and compromise patient health.[3]

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[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 near 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 (and this Court declined

I. The decision below exceeds the proper scope of judicial review and 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, threaten to block safe and effective drugs from getting to market, and prevent outdated conditions of use for approved drugs from being updated based on evolving scientific knowledge. Flexibility is a hallmark of the drug-approval process: Drug sponsors can leverage studies from many different sources, and those studies can reflect a wide range of designs, any of which can generate sufficient data to support approval. 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. Instead, these fact-specific issues require that FDA be able to flexibly exercise its medical and scientific expertise—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

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to grant review of that issue), the Fifth Circuit did so on statute-of-limitations grounds, not because it disagreed with the district court's arrogation to itself of the power to second-guess FDA's safety and effectiveness determinations.

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 asserted 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 rigidly mirrors the specific combination of conditions under which a drug will be used.

Such a requirement is unprecedented and has no legal basis. Under the framework set forth by

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

Congress, FDA evaluates the safety and effectiveness of a drug under its proposed conditions of use (and the impacts on safety and effectiveness of any changes proposed to approved conditions of use) using its expert scientific judgment. This flexibility is critical to ensuring that clinical studies can be tailored to specific drugs, diseases, and patient needs, and that they can be carried out ethically and efficiently.

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 it 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 that 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 must *always* consider 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*, 593 U.S. 357, 369 (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). The Fifth Circuit also stated that the record 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, even though FDA had carefully considered numerous clinical studies, several of which "considered 'multiple changes,'" Pet. App. 53a, and at least one of which considered *all* of the proposed changes in question. *See* Fed. Pet'rs Br. 38–39. Far from limiting the scope of its decision, the Fifth Circuit would broadly dictate the contours of clinical studies, effectively requiring a complete "match" between approved conditions of use and those of the supporting studies. This is a totally unworkable standard.

By inventing this novel requirement, with no statutory or regulatory basis, 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. *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). And its decision demonstrates a deep misunderstanding of

how clinical trial procedure and FDA review actually work.

FDA is not—and should not be—held to a heightened standard requiring it to justify every difference between studies and actual use; there are virtually always differences between clinical trial conditions and approved labeling. 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" for the purposes of demonstrating efficacy, safety, and that the benefits outweigh the risks. FDA, Framework for FDA's Real-World Evidence Program at 5 (Dec. 2018). Clinical trials thus must often have defined eligibility criteria in order to generate meaningful data; for example, patients with particular comorbidities may be excluded to avoid masking the effect of the drug. Similarly, clinical trials, especially early in development, often include monitoring procedures (*e.g.*, clinical and laboratory assessments) that go far beyond those that would (or should) apply in practice. Trial monitoring criteria are not required or expected to carry over into the approved labeling, and such a requirement (if even feasible under real-world conditions) would render real-world treatment unreasonably cumbersome, with no expected corollary patient benefit. Instead, as data on a drug's safety accumulates, necessary monitoring is adjusted accordingly. *See* FDA, Good Review Practice: Clinical Review of Investigational New Drug Applications (Dec. 2013). But that does not in any way mean that

FDA should be precluded from relying on properly generated clinical data in support of approvals.

The Fifth Circuit's approach disregards these longstanding practices and scientific realities. 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 for drugs utilizing cutting-edge technologies that rely on early clinical trials with conditions that inevitably will significantly differ from anticipated clinical practice.

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 with conditions that perfectly match the post-change conditions of use. And it would undermine FDA's ability to rely on data and information from real-world use to support post-approval changes. This inefficient and unworkable approach would freeze a drug's label in time, discourage innovation on existing products, and deprive patients of access to improved treatments. The inability to nimbly update labeling would be especially pernicious in therapeutic areas where disease states and scientific understandings evolve quickly, necessitating that drug sponsors and FDA constantly monitor the approved drug and submit sNDAs for needed updates and modifications. For example, updates may be necessary to reflect fast-moving evidence in the context of virus mutations, cancer, and development of 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 newly emerging or evolving diseases.

In addition, the Fifth Circuit's approach would make restrictions on newly approved drugs (such as those imposed through a Risk Evaluation and Mitigation Strategy, or "REMS") all but permanent, making it more difficult for FDA to do away with onerous restrictions even after real-world experience has demonstrated that they are unnecessary. This would negatively impact patient care and contravene Congress's instruction that FDA must continuously evaluate and monitor such restrictions and eliminate them when they become unnecessary for safe use and unduly burdensome on patient access or the healthcare system. *See* 21 U.S.C. § 355-1(f). If allowed to stand, the Fifth Circuit's approach could render drug development unworkable and freeze approved conditions of use in time, depriving patients of the benefits of evolving science and imposing outdated, unnecessary burdens on sponsors and healthcare providers.

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 the agency's decision to pare back certain restrictions on distribution of mifepristone. *See* Pet. App. 59a. The court did not find that FDA violated any statutory or regulatory requirement under the FDCA. Yet it concluded that FDA's actions were likely to be found

arbitrary and capricious, in part because it claimed FDA had "eliminate[d] a reporting requirement for a thing and then use[d] the resulting absence of data to support its decision." Pet. App. 59a (quotation marks omitted).[5]

That caricatured description bears no resemblance to reality. What really happened is that after fifteen years of intensive, enhanced monitoring, 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).

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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. 57a (quotation marks omitted). However, the FDCA expressly contemplates leveraging published literature to support approval decisions. *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.

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 and/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 data after a drug's approval. A drug 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.* (emphases added). This includes reports the sponsor receives from doctors and patients, "information derived from commercial marketing experience," "reports in the scientific literature," and even "unpublished scientific papers." *Id.* In addition, patients and healthcare providers routinely submit voluntary reports directly to FDA.

The Fifth Circuit declared 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. The court's reasoning thus calls into question whether FDA can *ever* rely on the FAERS system, creating doubt about FDA decisions beyond those at issue here and casting a pall of uncertainty over drug development and post-approval changes more generally. And by calling into question all safety data generated after the 2016 REMS modification, the Fifth Circuit could effectively prevent the agency from ever loosening additional reporting requirements imposed under a REMS—regardless of how

unnecessary and burdensome such requirements may be.

The decision below implies that the agency must impose unnecessary and overinclusive prescriber reporting requirements in order to support any future decision-making. This would deprive drug sponsors of the certainty and predictability of a stable system for post-approval adverse event reporting, 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), and erect another unnecessary barrier to updating approved drugs to keep pace with science.

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

The decision below represents a radical, unscientific departure from the reliance courts conducting arbitrary-and-capricious review normally and properly place on FDA's scientific and medical judgment. Congress intended that the nuanced benefit-risk judgments necessary for the drug-approval process be made by the politically accountable expert agency, not 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 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 benefit-risk approvability analysis without a hint of respect for the agency's scientific expertise in applying the statutory standards to particular facts and data. As discussed in more detail above, the court found fault 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 violates bedrock principles of arbitrary-and-capricious review under the APA. A court applying arbitrary-and-capricious review "is not to substitute its judgment for that of the agency." *State Farm*, 463 U.S. at 43; *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 who invest in it, and most importantly, the patients who depend on it.

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

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.

What the Fifth Circuit ignored is that 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 those 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. The Fifth Circuit's approach also would invite unnecessary litigation predicated on novel and unproven scientific theories.

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 companies and 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 decision-making 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, unless it is reversed, the Fifth Circuit's decision threatens a seismic shift in the clinical development, drug approval, and post-approval processes—erecting unnecessary and unscientific barriers to the approval of lifesaving medicines and critical improvements to them; chilling drug development and investment; threatening patient access to medicines; 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 reverse the judgment of the Fifth Circuit.

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