No. 23-10362

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

ALLIANCE FOR HIPPOCRATIC MEDICINE; AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS; AMERICAN COLLEGE OF PEDIATRICIANS; CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS; SHAUN JESTER, D.O.; REGINA FROST-CLARK, M.D.; TYLER JOHNSON, D.O.; GEORGE DELGADO, M.D.,

Plaintiffs-Appellees,

v.

U.S. FOOD & DRUG ADMINISTRATION; ROBERT M. CALIFF, Commissioner of Food and Drugs; JANET WOODCOCK, M.D., in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration;

(Caption continued on inside cover)

On Appeal from the United States District Court for the Northern District of Texas, Amarillo, No. 2:22-cv-223
Hon. Matthew J. Kacsmaryk, U.S. District Judge

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

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Defendants-Appellants,

v.

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CERTIFICATE OF INTERESTED PERSONS

Under Fifth Circuit Rule 29.2, the undersigned counsel of record for *amici curiae* certifies that the following listed persons and entities, in addition to those listed in the Appellants' Certificate of Interested Persons, have an interest in the amicus brief. These representations are made in order that judges of this Court may evaluate possible disqualification or recusal.

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Dated: May 1, 2023

/s/ Eva A. Temkin
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INTEREST OF *AMICI CURIAE*

Amici curiae are pharmaceutical companies, pharmaceutical company executives, and industry investors from across the United States. The district court's opinion would upend the application process (New Drug Applications, or "NDAs") that pharmaceutical companies use to seek Food and Drug Administration ("FDA") approval of new drugs. *Amici* collectively hold hundreds of approved NDAs and anticipate filing many more for drugs currently in development. *Amici* are therefore deeply familiar with the high costs associated with drug development and the need for regulatory clarity and certainty around drug approval, and are well positioned to explain to the Court the substantial chilling effect the district court's decision will impose on the development of new drugs.

A full list of *amici* is included as an Appendix to this brief.

The parties have consented to the filing of this *amicus* brief. No party or counsel for a party authored this brief in whole or in part. No party, counsel for a party, or person other than *amici*, their members, or their counsel made a monetary contribution intended to fund the preparation or submission of this brief.

INTRODUCTION

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 both safe and effective is the product of nearly a century of federal legislation delegating oversight of drug approvals to the FDA.

The district court's decision upends that longstanding statutory and regulatory framework. In issuing a "stay" of FDA's drug approval, the district court unreasonably found fault with FDA's sound scientific judgments. The court also badly misapplied governing drug-approval laws, and administrative law more generally, including by (i) substituting personal conclusions—drawn from anecdotes and cherry-picked publications—for FDA's rigorous, data-driven scientific analysis; (ii) ruling, without scientific or legal basis, that FDA must require a clinical trial under conditions that perfectly match the drug's labeling (including evaluating any changes in combination with each other) or else provide a special justification for not doing so; (iii) finding FDA's treatment of adverse event data to be improper under an incorrect (and

impossible) standard; (iv) opining, without scientific or legal basis, that expensive and impractical studies comparing two treatments head-to-head are necessary to demonstrate meaningful therapeutic benefit; and (v) unnecessarily adopting an improperly narrow interpretation of what constitutes a serious or life-threatening illness and ignoring intervening amendments to the Federal Food, Drug, and Cosmetic Act ("FDCA").

The district court's order would sharply restrict (if not completely eliminate) 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 district court's logic would create chaos for the drug-approval process, not least by inviting any plaintiff to challenge the approval of any drug, regardless of how long the drug has been on the market or how spurious the grounds. Any patient, whether or not they actually suffer side effects, or any physician, whether or not they actually treat any such patient, could ask a judge to undermine patient access to any drug nationwide, based on nothing but conjecture and cherry-picked publications. That outcome would chill crucial research and development, undermine the viability of investments in this important sector, and wreak havoc on drug development and approval generally—

all of which would irreparably harm patients, providers, and the entire pharmaceutical industry.

Accordingly, *amici* urge this Court to reverse the district court's order.

BACKGROUND

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

Since its enactment nearly a century ago, the 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 early 1960s, Congress added a further pre-marketing 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 dual requirements of safety and efficacy are the touchstones of FDA review. And over the last sixty years, Congress has repeatedly expanded FDA's authority and affirmed FDA's role as the sole arbiter of whether and how 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 provisions and regulations as guardrails, FDA has retained significant flexibility in the drug-approval process—flexibility that is essential to allow FDA to apply its expert scientific and medical judgment on a case-by-case basis.

Because all drugs have the potential for adverse effects, demonstrating a drug's safety does not require that a sponsor show that a 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 constitutes the core of FDA's drug-approval standard and was entrusted by Congress to FDA, as the expert agency, not to the courts.

B. The statute and regulations require painstaking demonstrations of 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 seek approval of an NDA, the drug sponsor undertakes a lengthy and resource-intensive development program. As part of that program, it performs rigorous scientific studies and analyses to demonstrate the drug's safety and efficacy and to develop physician labeling. Those studies and analyses include laboratory testing; preclinical (animal) testing; three separate phases of rigorous clinical studies involving, on average, several thousand patients; and

development of chemistry, manufacturing, and controls information. Scientific and medical experts at FDA participate throughout the process, which culminates when the sponsor submits, and FDA reviews, the NDA.

FDA's decision to approve an NDA is complex and predicated on a rigorous process requiring particularized expertise. FDA will approve an NDA only if the applicant demonstrates that the drug is safe and effective for the proposed use or uses and there is no other ground for denial. 21 U.S.C. § 355(c)(1). If the application does not demonstrate that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the proposed labeling, FDA must refuse to approve the NDA. *Id.* § 355(b) & (d)(1), (2), (4), (5); 21 C.F.R. § 314.50(a)(1).

The Subpart H regulations. In 1992, FDA promulgated regulations to enhance the agency's flexibility with respect to (1) the kinds of evidence that FDA could rely on to make the requisite finding of effectiveness in support of NDA approval, and (2) the tools FDA had at its disposal to ensure positive benefit-risk calculations for particular drugs.

All drugs approved using the Subpart H tools meet the requisite standards for approval. *See generally* Final Rule: New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992). In addition to its better known accelerated-approval provisions, Subpart H also gave FDA flexibility to impose conditions "needed to assure safe use," including distribution restrictions, on drugs that were intended to treat "serious or life-threatening illnesses," that "provide[d] meaningful therapeutic benefit to patients over existing treatments," and that otherwise satisfied the requirements of the FDCA. *Id.* at 58,958 (codified at 21 C.F.R. §§ 314.500, 314.520). Far from disfavoring this approach to making important drugs available to the public, Congress later codified these tools into the FDCA. 21 U.S.C. §§ 355-1, 356(c).

Adverse event reporting. FDA regulations require all NDA holders to review adverse drug experience information received from any source and to report fatal *and* non-fatal adverse events to FDA. 21 C.F.R. § 314.80. With only a handful of exceptions, all known adverse drug experiences must be reported to FDA; the only differences are with respect to when, not whether, they must be reported. *Id.* In particular,

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"), the adverse drug experiences that must be reported within this time frame include 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). NDA holders also must report other adverse events 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).

On occasion, FDA can require yet additional adverse event reporting, for example by requiring physicians to report certain types of adverse events. *See* 21 U.S.C. § 355-1(f)(3). When FDA does so, the agency must periodically to reassess such requirements, and must pare them back, as appropriate, in light of evaluations and input received from

patients, physicians, pharmacists, and other healthcare providers, *id.* § 355-1(f)(5), and as necessary to "minimize the burden on the health care delivery system," *id.* § 355-1(g)(4)(B).

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, 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 new and cutting-edge technologies.

Drug development entails massive expense and considerable business risk. Only about 12% of drugs entering clinical trials are ultimately approved, and the cost of developing a new drug can exceed two billion dollars. *See* Cong. Budget Office, No. 57025, Research and Development in the Pharmaceutical Industry, at 2 (Apr. 2021), *available at* https://www.cbo.gov/publication/57126. Because of that inherent unpredictability, investors in drug development depend on the clarity and stability of FDA's scientific decision-making with respect to drug approvals. That clarity and stability provide much-needed certainty for investors, who in turn provide the investments that lead to the

development of new, important, and potentially lifesaving drugs for the patients who need them.

ARGUMENT

The district court ruled that FDA's approvals of the mifepristone NDA and 2016 supplemental NDA, as well as FDA's 2021 decision to exercise enforcement discretion with respect to certain distribution restrictions, violated the FDCA and the Administrative Procedure Act ("APA"). In reaching those conclusions, the district court substituted its own idiosyncratic views of clinical benefit and safety for the gold-standard benefit-risk analysis required by Congress and performed by FDA's medical and scientific professionals. In so doing, the court ignored the flexibility the FDCA deliberately affords FDA—with its expert scientific judgment—in making safety and efficacy decisions. Instead of appropriately deferring to FDA's scientific expertise, and in lieu of the approval standards established by Congress and implemented by FDA, the court invented its own novel, unworkable standards to govern drug development and approval.[1]

[1] Similarly, the district court's rewriting of bedrock caselaw regarding Article III standing would throw open the doors of the federal courts to

I. The district court improperly substituted its own views for FDA's expert scientific judgment.

The district court's decision represents a radical departure from the deference courts normally and properly show 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 significant deference to the politically accountable entities with the background, competence, and expertise to assess public health." (quotation marks omitted)).

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challenges to any drug brought by any patient, whether or not they actually suffer side effects, or by any physician, whether or not they actually treat any such patient. Appellants thoroughly explain the fundamental errors in the district court's conclusion that plaintiffs have standing. If accepted, the speculative standing argument here could be applied to virtually any other FDA-approved drug. The district court's sweeping expansion of standing would enable limitless challenges to FDA-approved drugs, and the resulting instability would undercut drug development and investment.

The district court faulted FDA for not denying the mifepristone NDA under section 505(d) of the FDCA, which requires FDA to deny an application if it does not "include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d). But it did not find that FDA failed to apply that standard. Nor did it identify any errors in FDA's scientific judgment or calculations. Instead, the court proffered its own, competing analysis, which lacked any evidence that could support the type of rigorous scientific decision-making with which FDA is tasked (and which it carried out here). The court cast aside not only the voluminous scientific evidence FDA considered at the time of approval, but also nearly a quarter-century of subsequent data that FDA determined confirmed the drug as safe and effective. In its place, the court cherry-picked personal stories told by plaintiffs and unreliable publications (including anonymous blog posts), many of which were not even submitted to FDA. The court then ruled that FDA was required to deny the NDA based on the court's own non-scientific assessment of this alternative record.

This result conflicts with the FDCA and the APA and violates bedrock principles of administrative law. 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"). If affirmed, the district court's non-expert, judicial second-guessing of FDA's scientific judgment regarding NDA approvability threatens turmoil for the industry, those that invest in it, and most importantly, the patients who depend on it.

II. The district court's decision would create impossibly rigid new standards for drug development and approval.

Not only did the district court improperly refuse to defer to FDA's expert judgment, it also adopted novel and inflexible requirements to govern the drug-approval process. Nothing in the FDCA mandates the new and rigid requirements the district court imposed, or otherwise prevents FDA from applying its expert judgment to assess the adequacy

of the scientific evidence presented to support approval of an NDA or a labeling change.

To the contrary, one hallmark of the drug-approval process is its flexibility. Drug sponsors can leverage studies from many different sources, even in lieu of conducting clinical studies. *See* 21 U.S.C. § 355(b)(2). Moreover, those studies can reflect a wide range of designs, because an NDA is required only to contain *sufficient* data to demonstrate the drug's safety and effectiveness. 21 C.F.R. § 314.50. Neither Congress nor FDA has imposed artificial or unnecessary limits on what form that data must take. This flexibility is crucial, not least because not all disease states or treatments lend themselves to particular study designs. *See, e.g.*, Sundeep Agrawal et al., *Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002-2021*, 9 JAMA Oncology 266 (2023) (reviewing approved marketing applications based on single-arm trials). It reflects Congress's considered decision to rely on FDA's expertise in distinguishing robust and reliable data from colorful but clinically and statistically meaningless (and potentially misleading) anecdotes—disaggregating signal from noise in the inputs it receives.

The district court's inflexible approach also would have ripple effects across FDA's programs for drugs intended to treat serious and life-threatening diseases and conditions—programs that are essential to facilitating and expediting the development and review of critical medicines. It could narrow eligibility for these programs, delay patient access to important and potentially lifesaving medications, and discourage development of medications in the first instance. Without sufficient flexibility, sponsors would lose considerable efficiency in bringing new drugs to market, and in updating and improving on existing approved applications. And that in turn would come at the expense of patients, who would lose access to treatments that can improve or even save their lives.

A. The district court improperly imposed rigid labeling and comparative-trial requirements.

Ignoring the plain statutory text and structure of the FDCA, FDA's duly promulgated regulations, and decades of precedent, the district court found that FDA had acted arbitrarily and capriciously in failing to match the conditions of use in the drug's FDA-approved labeling with those in the supporting clinical trials. *See* ROA.4357, ROA.4363–4364. Specifically, although the district court acknowledged that the FDCA

does not *require* the conditions of use approved in a drug's labeling to "match" the conditions in any clinical trials supporting approval, ROA.4356 n.48, ROA.4366, the court nevertheless ruled that FDA was required to provide a detailed explanation for not incorporating all of the clinical trial conditions into the labeling—and that it had acted arbitrarily and capriciously by not doing so. ROA 4357–4364.

The district court did not ground This conclusion in any statutory or regulatory text; rather, it improperly recast deferential arbitrary-and-capricious review as an opportunity to "substitute its judgment" for that of the expert agency. *State Farm*, 463 U.S. at 43. Through this misuse of arbitrary-and-capricious review, the district court effectively rewrote the FDCA's drug-approval paradigm, requiring FDA to support every aspect of a drug's approved labeling—and every change to that labeling—with a clinical trial that studies the precise conditions of use at issue. Its reasoning would create a presumption that a drug's labeling must include precisely the same conditions as the randomized clinical trials that provide the basis for approval, unless FDA "cogently explain[s]" any differences. ROA.4366 (quotation marks omitted). That presumption has no basis in law or in fact. Indeed, the only "support" the district court

mustered came from one university's Institutional Review Board glossary page—not from any statute, regulation, or agency guidance. *See* ROA.4355 & n.46. The court failed to recognize that 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.

Similarly, the district court concluded that FDA acted arbitrarily and capriciously by failing to cite "studies compar[ing]" the safety of proposed labeling changes "against the then-current regimen." ROA.4365. Instead, the court simply invented a novel rule that even though FDA had evaluated the proposed labeling changes, FDA's approval of the changes was arbitrary and capricious because it did not examine the potential safety consequences of those changes under the precise conditions of use that would exist if the changes were made. The court thus suggested that a labeling change is permissible only if supported by a clinical trial that perfectly compares the pre- and post-change conditions—or, as the motions panel termed it, "studies that evaluated the safety-and-effectiveness consequences of [those changes]

as a whole." ROA.4412. Again, the district court did not cite any authority for this requirement, and, again, none exists.

Clinical trials—and particularly randomized, controlled clinical trials—are simply 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). This is true of both clinical trials intended to support initial NDA approval and those intended to support subsequent changes.

As FDA and the sponsor learn more about the drug through additional development, the clinical trial parameters evolve—as they should—to reflect new knowledge. Clinical trials often have restrictive eligibility criteria and additional monitoring procedures beyond those that would apply in clinical practice. For example, FDA has identified numerous strategies to adopt selection criteria that improve the power and practicality of a clinical trial, such as requiring persistence of a disease over a run-in period; stability of baseline measures such as blood pressure, exercise tests, or pulmonary tests; or factors that improve the

likelihood of compliance. FDA, Good Review Practice: Clinical Review of Investigational New Drug Applications (Dec. 2013). But these selection criteria are not required or expected to carry over into the approved labeling.

The district court's approach disregards FDA's longstanding flexibility and would instead require FDA to justify each and every difference between the labeling and the trial conditions, encouraging judicial second-guessing of FDA's sound and reasoned judgments. Among other problems, such a requirement would result in inappropriately narrow labeled indications, which would unnecessarily limit patient access. It also would create an avenue for parties to challenge FDA's decision any time the agency does not require a precise match between labeling and trial conditions—which is essentially every time FDA approves a drug.[2]

[2] The district court suggested in passing that FDA's 2000 approval of mifepristone may have been arbitrary and capricious because the drug was not "tested for under-18 girls undergoing reproductive development" even though such testing may have, in the court's opinion, been required under the Pediatric Research Equity Act ("PREA") and the FDA regulations that preceded it (known as the "Pediatric Rule"). ROA.4357 & n.49. That brief suggestion bears little weight. As the district court acknowledged, a court subsequently determined the Pediatric Rule

This novel framework, which appears nowhere in the text of the FDCA that two houses of Congress passed and the President signed, is rigid, unworkable, and entirely unnecessary. For example, in early clinical trials, the conditions imposed inevitably and significantly differ from anticipated clinical practice. Under the district court's rule, a sponsor could therefore not rely on early efficacy studies to provide substantial evidence of effectiveness—thus invalidating a common practice for cutting-edge technologies and drugs for rare diseases, among others.

Incremental improvements to approved drugs (including new indications) are also often supported by multiple types of studies and data, and there is no requirement that a drug can only be approved, or

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exceeded FDA's authority. And PREA, which was enacted in 2003, does not require a drug sponsor to conduct separate pediatric studies (nor did the Pediatric Rule before it). To the contrary, FDA can rely on extrapolation or waiver to satisfy the statutory conditions for approval or can defer the obligation. *See* 21 U.S.C. § 355c; 21 C.F.R. § 314.55(a).

In any case, FDA further explained in 2016 why no additional pediatric studies were required under PREA, *see* FDA, New Drug Application No. 020687/S-020, Summary Review, at 17–19 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020SumR.pdf, and the district court did not even address that explanation, much less find it arbitrary or capricious.

its labeling can only be modified, if supported by particular types of clinical trials—let alone trials conducted under conditions that perfectly match the labeling or that evaluate changes "*as a whole*." ROA.4412. Similarly, post-approval labeling changes are a common and necessary part of approval maintenance. The district court's approach would hinder reliance on even new data and information to support post-approval innovations and other changes unless the trial conditions perfectly matched the labeling changes. This would be an impossible burden. Under this approach, FDA could no longer approve such changes without costly, time-consuming, and unnecessary studies. This approach would also freeze drug labeling in time, discourage sponsors from continuing to innovate on their existing products, and deprive patients of access to improved treatments. The district court's reasoning would also make it more difficult for FDA to do away with onerous restrictions that real-world experience has demonstrated are not necessary, which would make access to critical drugs more difficult than it should be.[3]

[3] The inability to nimbly update labeling would 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

B. The district court's decision undermines FDA's ability to generate and rely on useful safety data.

The district court also found fault with FDA's reliance on data from the FDA Adverse Event Reporting System ("FAERS"), a database containing reports of adverse events experienced by patients while using an approved treatment, both in order to pare back additional reporting requirements that had previously been imposed and for regulatory decision-making thereafter. *See* ROA.4344–4345. Once again, the district court did not find that FDA violated any specific statutory or regulatory requirement; it found only that FDA's actions were (in the district court's view) arbitrary and capricious. But FDA's actions were entirely reasonable exercises of its authority and expertise, especially in light of the agency's long experience with the drug in question. What really happened here (as opposed to what the district court incorrectly claimed happened) is that after *fifteen years* of unusually intensive monitoring firmly established the drug's strong safety profile, FDA

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moving evidence in the context of virus mutations and developing antimicrobial resistance. The district court's rigid requirements would undermine under the ability to make these critical updates, and FDA (and patients) would be left with decades-old tools in fights against modern diseases.

determined that certain *extra* reporting was no longer warranted. It therefore pared back the heightened reporting requirements for non-fatal adverse event reporting it had previously imposed under the REMS, as it was required to do. *See* 21 U.S.C. §§ 355-1(f), (g).

There is no legal basis whatsoever for the district court's suggestions that this action was unreasonable or that it rendered the post-2016 FAERS data unusable without additional physician reporting requirements. Contrary to the district court's assertion, this change did *not* "practically eliminate an 'adverse event' reporting requirement." ROA.4345. Quite the contrary: as FDA explained, the applicant would "still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports" and to submit periodic adverse drug experience reports for virtually all other known adverse events. FDA, New Drug Application No. 020687/S-020, Medical Review, at 8 (Mar. 29, 2016), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf; *see also* FDA, New Drug Application No. 020687/S-020, REMS Modification Review, at 10 (Mar. 29, 2016), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RiskR.pdf

(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). These requirements are extensive, obligating NDA holders to review "*all* adverse drug experience information" received from "*any* source." This includes, but is not limited to, commercial marketing experience, reports in the scientific literature, and even unpublished scientific papers. 21 C.F.R. § 314.80(b) (emphasis added). It also includes voluntary reports routinely submitted to FDA by patients and healthcare providers. The district court's assertion that the relevant database was designed to "produce a null set," ROA.4345, *i.e.*, that it deliberately turned a blind eye to safety issues, fundamentally mischaracterizes these comprehensive reporting requirements that apply to nearly every approved drug and ignores the information that those requirements generate.

The district court's reasoning would require FDA to impose unnecessary and overinclusive reporting requirements on prescribers and drug sponsors—rather than complying with the statutory mandate that it pare back unnecessary and unduly burdensome requirements. It

drastically underappreciates the utility of data from FAERS, itself a critical source of safety information, instead suggesting that FDA cannot rely on FAERS data alone without opening itself up to litigation. This path would impose unnecessary costs on industry without furthering the fundamental purpose of adverse event reporting. Yet again, the district court misused arbitrary-and-capricious review to substitute its own judicially-crafted scheme, unmoored from any statutory or regulatory text, for that of the expert agency.

C. The district court badly misinterpreted and misapplied Subpart H.

The district court devoted much space to plaintiffs' claims challenging FDA's application of the Subpart H regulations twenty-three years ago, claims that would also have significant implications in particular for drugs that treat rare diseases. The court did so even though there was no need for it to interpret the Subpart H regulations (including the terms "meaningful therapeutic benefit" and "serious or life-threatening illness") at all. For more than fifteen years, the mifepristone distribution restrictions have been imposed under 21 U.S.C. § 355-1, which does not include those limitations and which applies to any drug for which the agency concludes additional regulation is

necessary to ensure a positive benefit-risk balance. Yet the district court needlessly reached out to decide these issues under the Subpart H regulations, and its mistaken decision could have serious negative implications for other programs under the FDCA.

"Meaningful therapeutic benefit." Whether a drug confers a meaningful therapeutic benefit to patients is a matter of scientific judgment and depends on the magnitude of the drug's effect and the importance of that effect to treatment of the patient's condition. These matters call for application of the agency's expertise. The district court, however, rejected FDA's determination that the drug in question conferred a meaningful therapeutic benefit. Instead, the court concluded that a meaningful therapeutic benefit cannot be found absent a clinical trial comparing treatments. *See* ROA.4350–4353. That, too, was error.

There is no legal requirement that "meaningful therapeutic benefit" be demonstrated by any particular type of study, or by a particular comparison with alternatives. Quite the contrary: as with clinical-study designs, FDA exercises appropriate discretion in determining meaningful therapeutic benefit, and findings of meaningful therapeutic benefit are often made even in the absence of any existing approved treatment to

which the drug in question can be compared. *See* FDA, Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics, at 16 (May 2014) (noting that "[a]mended section 506(c) [of the FDCA] clarifies the Agency's flexibility," including when determining whether a drug provides a meaningful advantage).

Although the NDA in question here was not approved under an expedited program, a number of those programs require FDA to consider the proposed drug in the context of other treatments, if any exist. *See, e.g.*, 21 U.S.C. § 356(c)(1)(A) (FDA must "tak[e] into account … the availability or lack of alternative treatments"). FDA's discretion to determine whether a drug confers a meaningful benefit is a critical element of numerous FDCA programs, including breakthrough therapy designation (21 U.S.C. § 356(a)), accelerated approval (21 U.S.C. § 356(c)), and priority review designation (*see* Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491), all of which are vital for drug developers to ensure funding and attain regulatory engagement.

Head-to-head studies, *i.e.*, direct comparative studies of two different treatments for the same indication, are often technically difficult, expensive, and impractical. Moreover, in areas of unmet

medical need, there may be no alternative treatment against which such a study could even be conducted. And in some circumstances—for example, with regard to oncology treatments for terminal patients—ethical considerations may preclude conducting head-to-head clinical trials. For all of these reasons, requiring head-to-head clinical data as a prerequisite to expedited programs is contrary to the purpose of these programs, which is to catalyze drug development in areas where patients have the fewest options.

The type of second-guessing in which the district court engaged—in violation of established principles of administrative law—would inject an intolerable level of uncertainty into FDA's determinations in this area. This Court should reaffirm that FDA enjoys the flexibility to determine "meaningful therapeutic benefit" based on its expert judgment, with or without head-to-head data—and that it is eminently reasonable for the agency to conclude that a non-surgical treatment provides a "meaningful therapeutic benefit" over a surgical one.

"Serious" or "life-threatening illness." Similar to "meaningful therapeutic benefit," various FDCA programs require FDA to assess whether a drug is intended to treat a "serious" or "life-threatening"

disease or condition. *E.g.*, 21 U.S.C. § 356; 21 C.F.R. § 314.500. FDA enjoys considerable discretion in implementing these programs.

Instead of deferring to FDA's medical expertise, however, the district court unreasonably limited FDA's discretion by adopting a cramped interpretation of the terms "serious" and "life-threatening," as well as drawing an artificial distinction between an "illness" and a "condition." The district court's interpretations would prevent FDA from considering serious complications or negative experiences associated with a disease or condition in determining whether it is "serious" or "life-threatening." ROA.4346–4347; ROA.4350. Taken together, these interpretations could unnecessarily restrict consideration of certain drugs for other FDA programs intended to spur drug development for serious and life-threatening illnesses. And again, no legal authority justifies the district court's novel restriction on FDA's discretion and exercise of its scientific judgment, which would undermine settled FDA practices and the industry research, development, and investment that rely on those practices.

III. The district court's transformation of FDCA requirements would chill drug development and investment.

Regulatory flexibility and respect for FDA's scientific judgment are crucial to fostering development of new and innovative drugs in all the ways discussed above and more. FDA has exercised this critical flexibility in approving thousands of drugs, including numerous transformative medicines. Had those drugs been developed or reviewed by FDA under the district court's approach, it is unclear which, if any, would have been approved—or that their approvals would have been unchallenged in court—and countless patients would have suffered needlessly as a result.

If the district court's unworkable standards were adopted going forward, drug developers would have to conduct trials using *only* the conditions of use for which inclusion in labeling would be appropriate (and only for those patients for whom the drug ultimately might be indicated) or else run the risk that a court might reverse FDA's approval of those conditions, decades later and without any scientific justification. This untenable approach would pose significant obstacles to designing clinical trials. It would limit the utility of early efficacy studies and raise questions about the utility of other kinds of studies, like bioequivalence

and bioavailability studies, to support marketing applications, since the ultimately approved labeling will virtually always differ from the conditions of use in those trials. It would also ossify labeling, excluding new information gathered from outside the original clinical trials and threatening further innovations.

In addition, development of drugs that depend on FDA programs reserved for drugs expected to confer meaningful therapeutic benefit, including many for rare diseases, would collapse under the weight of the district court's new head-to-head study requirement. And, with the district court's narrowing of FDA's discretion to determine whether a drug is intended to treat a "serious" or "life-threatening" disease or condition, many drugs would no longer be eligible for programs that incorporate those requirements, delaying their availability to patients or even discouraging their development altogether.

In these ways and others, the district court's decision would 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. By improperly second-guessing FDA's scientific judgment, and by imposing new and unwarranted restrictions on the exercise of that judgment, the district court's decision threatens to destabilize FDA approval decisions, even decades after a drug's approval. 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, if allowed to take effect, the district court's opinion would result in 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 long-standing drug approval process, which is rooted in science and law.

CONCLUSION

For the reasons set forth above, this Court should reverse the district court's order.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I certify that on May 1, 2023, the foregoing Brief of Pharmaceutical Companies, Executives, and Investors as *Amici Curiae* in support of Appellants has been served via the Court's ECF filing system in compliance with Rule 25(b) and (c) of the Federal Rules of Appellate Procedure on all registered counsel of record and has been transmitted to the Clerk of the Court.

I further certify that a copy of the foregoing was served via First-Class U.S. Mail upon the following unregistered counsel:

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CERTIFICATE OF COMPLIANCE

This brief complies with Fed. R. Civ. P. 29(a)(5) contains 6,217 words, as counted by Microsoft Word, excluding the parts of the brief excluded by Fed. R. App. P. 32(f). This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6) because it has been prepared using Microsoft Word in Century Schoolbook 14-point font.

I further certify that (1) required privacy redactions have been made, 5th Cir. R. 25.2.13; (2) the electronic submission is an exact copy of the paper document, 5th Cir. R. 25.2.1; and (3) the document has been scanned with the most recent version of Microsoft Defender and is free of viruses.

Dated: May 1, 2023

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