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.

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' MOTION FOR STAY PENDING APPEAL

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April 11, 2023

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Defendants-Appellants,

v.

DANCO LABORATORIES, L.L.C.,

Intervenor-Appellant.

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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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* Ms. Devendorf's admission to practice law in the State of New York is pending; she is practicing with the direct supervision of the firm's principals.

Dated: April 11, 2023

/s/ Eva A. Temkin
Eva A. Temkin

Counsel for Amici Curiae

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Regulations

Other Authorities

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 NDAs and anticipate filing many more 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.

No fees have been paid or will be paid for the preparation and filing of this *amicus* brief.

SUMMARY OF ARGUMENT

Each year, pharmaceutical developers and investors devote billions of research and development dollars to creating new safe and effective medications to treat diseases and improve lives. In the United States, the process by which those drugs are tested to ensure that they are both safe and effective is the product of nearly a century of federal legislation delegating drug-approval oversight to FDA.

The district court's decision is at odds with that longstanding statutory and regulatory framework. The district court unreasonably found fault with FDA's sound scientific judgments in order to stay approval of a drug that has been approved for nearly a quarter-century and used safely by millions of women. 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) holding, without legal basis, that FDA must provide a special justification for any differences between a drug's labeling and the conditions that existed in the drug's clinical trials; (iii) opining, without scientific or legal basis, that head-to-head studies

are necessary to demonstrate meaningful therapeutic benefit; (iv) holding FDA's reliance on adverse event data to be improper under an incorrect (and impossible) standard; and (v) adopting an improperly narrow interpretation of what constitutes a serious or life-threatening illness and ignoring intervening amendments to the FDCA.

Far from being limited to one drug, the logic of the district court's order overturns the long-settled legal basis of FDA's drug-approval process. Unless stayed, the district court's lawless opinion will empower any plaintiff to grind drug approvals to a halt, disrupting patients' access to critical medicines. 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, causing widespread harm to patients, providers, and the entire pharmaceutical industry. Indeed, hundreds of industry members have already signed a public letter arguing that the district court's decision "has set a precedent for diminishing FDA's authority over drug approvals" and "create[d] uncertainty for the entire biopharma industry," and calling for the decision to be reversed. *See* Letter Petition in Support

of FDA's Authority to Regulate Medicines (Apr. 7, 2023), https://docsend.com/view/2ahvmwy8djzxax3g.[1]

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

ARGUMENT

I. FDA's Scientific and Medical Judgments Regarding Drug Approval Decisions Should Not Be Second-Guessed by Courts that Lack Similar Expertise.

A. Congress Intended FDA, Not the Courts, to Serve as the Expert Arbiter of the Safety and Effectiveness of Drugs.

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 early 1960s, Congress added a further pre-marketing requirement that FDA determine a drug is 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.).

[1] This brief focuses on the district court's holdings that pose the greatest threat to drug development; it does not address all of the district court's erroneous holdings.

With these dual requirements of safety and efficacy as the touchstone of FDA review, 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 has promulgated regulations that describe the scientific principles of adequate and well-controlled clinical investigations and the requirements for labeling of approved drugs (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.

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 typically undertakes a lengthy and resource-intensive development program. It performs rigorous scientific studies to demonstrate the drug's safety and efficacy, including: laboratory testing; preclinical (animal) testing; three separate phases of clinical studies averaging 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 a new drug application is complex and is predicated on a rigorous process requiring particularized expertise. Only if the applicant demonstrates that the drug is safe and effective for the proposed use(s), and there is no other ground for denial, will FDA approve the application. 21 U.S.C. § 355(c)(1). Conversely, FDA will refuse to approve an NDA 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. *Id.* § 355(b) & (d)(1), (2), (4), (5); 21 C.F.R. § 314.50(a)(1).

Because all drugs have the potential for adverse effects, demonstrating a drug's safety does not require that a sponsor show an absence of potential adverse effects, but rather that the drug's benefits outweigh any risks it poses. 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, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs."); 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 balance between benefits and risks constitutes the core of FDA's drug approval standard.

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 more widely recognized accelerated approval provisions, Subpart H allowed FDA to impose conditions "needed to assure safe use," including distribution restrictions, on drugs 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 balancing approach to making important drugs available to the public, Congress subsequently codified these tools in the FDCA. 21 U.S.C. §§ 355-1, 356(c).

C. FDA's Drug Review Is the Gold Standard of Scientific Review.

FDA's drug review process is recognized as the "gold standard" worldwide, 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. Accordingly, clarity and predictability in FDA's review and approval process is particularly important for drug development, which presents considerable expense and business risk, and for incentivizing investment in such development. [2]

II. The District Court's Order Misapprehends the Drug Approval Framework and Imposes Unworkable Standards that Will Upend Drug Development and Harm Patient Access.

The district court ruled that FDA's approvals of the mifepristone NDA and 2016 supplemental NDA violated the FDCA and the Administrative Procedure Act. In doing so, the court substituted its own idiosyncratic views of clinical benefit and safety, replacing the gold-standard benefit-risk analysis and expert judgment of FDA's medical and

[2] Only about 12% of drugs entering clinical trials are ultimately approved, with recent studies estimating that R&D costs can exceed $2 billion per drug. *See* Cong. Budget Office, No. 57025, Research and Development in the Pharmaceutical Industry 2 (Apr. 2021), *available at* https://www.cbo.gov/publication/57126.

scientific professionals with anecdotes and conjecture. The court also misapprehended the degree of flexibility the FDCA affords FDA—with its expert scientific judgment—in making safety and efficacy decisions. Instead of appropriately deferring to FDA's scientific expertise, the district court instead crafted novel, unworkable standards to govern drug development and approval.

A. Approved Labeling Cannot Be Limited to the Precise Conditions of Use Studied in Clinical Development.

Ignoring the plain statutory text of the FDCA, FDA's duly promulgated regulations, and decades of precedent, the district court found that FDA acted arbitrarily and capriciously in failing to match the conditions of use in the FDA-approved labeling with those in the supporting clinical trials. *See* Dkt. 137, Memorandum Opinion and Order (Apr. 7, 2023) ("Op.") 51, 57–58. The district court acknowledged that the FDCA does not require the conditions of use approved in the labeling to "match" the conditions in the clinical trial supporting approval. Op. 50 n.48, 60. The court nevertheless ruled that FDA had acted arbitrarily and capriciously because it did not provide a detailed explanation for not incorporating all of the clinical trial conditions into the labeling. *See* Op. 51–58.

In so holding, the district court effectively transformed the drug-approval paradigm, requiring FDA to justify each departure from clinical trial conditions in approved labeling.The district court thus effectively created a presumption that a drug's labeling must include precisely the same conditions as the clinical trials that supported approval, unless FDA "cogently explain[s]" any differences. Op. 60 (quotation marks omitted). That presumption has no basis in law.[3] 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 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" and are "designed to control variability and maximize data quality." FDA, Framework for FDA's Real-World Evidence Program at 5 (Dec. 2018). As FDA and the sponsor learn more about the drug through additional development, the trial parameters evolve to reflect new knowledge. Thus, clinical trials

[3] 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* Op. 49 & n.46.

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 strategies are not required or expected to carry over into the approved labeling.

The district court's approach would disregard this longstanding practice and 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. It would also 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—essentially *every* time FDA approves a drug. This framework is rigid and unworkable. 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—a common practice for cutting-edge technologies and drugs for rare diseases, among others.

B. The Court Was Wrong to Substitute Its Own Views for FDA's Scientific Judgment Regarding a Drug Approval.

In relevant part, section 505(d) of the FDCA 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).

The district court faulted FDA for not denying the mifepristone NDA under this standard. However, the opinion identified no 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. 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 showing safe and effective use of the drug. In its place,

the court relied on personal stories told by plaintiffs and cherry-picked, unreliable publications—many of which were not even submitted to FDA. The court then ruled that FDA was required to refuse to approve the NDA based on the court's own non-scientific assessment of this alternative, incomplete record.

This result is contrary to the statute, and it violates bedrock principles of administrative law. Left standing, this non-expert, judicial second-guessing threatens to cause turmoil for the industry and those that invest in it, and for patients as well.[4]

[4] 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" notwithstanding FDA's "Pediatric Rule" and the subsequently-enacted Pediatric Research Equity Act ("PREA"). Op. 51 & n.49. That brief suggestion bears little weight. The district court acknowledged that a court subsequently determined the Pediatric Rule exceeded FDA's authority. And PREA, like the Pediatric Rule before it, does not necessarily require a drug sponsor to conduct separate pediatric studies; for example, 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. FDA 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 hold that it was arbitrary or capricious.

C. The District Court's Order Would Create Impossibly Rigid New Standards for Drug Development and Approval.

When second-guessing FDA's expert review, the district court also took an inexplicably rigid approach to interpreting and applying the statutory and regulatory requirements. But nothing in the FDCA mandates such rigid requirements on study design or otherwise prevents FDA from applying its expert judgment to assess the adequacy of the scientific evidence presented in individual NDAs. To the contrary, NDA applicants can leverage studies from many different sources, even in lieu of conducting clinical studies. *See* 21 U.S.C. § 355(b)(2). Clinical studies can reflect a wide range of designs; an NDA is required only to contain sufficient data to demonstrate the drug's safety and effectiveness. 21 C.F.R. § 314.50. This flexibility is crucial, including 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).

The district court's approach 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 would narrow eligibility for these programs, delay patient access to life-saving medications, and discourage development in the first instance. Without sufficient flexibility, sponsors would lose considerable efficiency in bringing new drugs to market—and in updating and innovating on existing approved applications. And patients would lose access to potentially lifesaving and life-improving treatments.

1. The District Court Wrongly Suggested that Head-to-Head Studies Are Needed to Demonstrate "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 the 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* Op. 44–47. 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. *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. *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.

Requiring head-to-head clinical data as a prerequisite to these expedited programs would render them meaningless. And 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. Moreover, ethical considerations may preclude conducting head-to-head clinical trials, for example, in oncology treatments for terminal patients. This Court should affirm that FDA enjoys the flexibility to determine "meaningful therapeutic benefit" through the application of its expert judgment, with or without head-to-head data—and that a non-surgical treatment can provide a "meaningful therapeutic benefit" over a surgical one.

2. Innovations and Labeling Updates Do Not Require Specific Types of Comparative Trial Data.

The district court also concluded that FDA acted arbitrarily and capriciously by failing to compare the safety of proposed labeling changes

"against the then-current regimen." Op. 59. 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. The court cited no authority for this requirement—and none exists. Incremental improvements to approved drugs (including new indications) are often supported by multiple types of studies and data. Under the district court's approach, FDA could no longer approve such changes without requiring costly, unjustified studies. The district court's approach would freeze drug labeling in time, discourage sponsors from continuing to innovate on their existing products, and deprive patients of access to improved treatments.

Similarly, post-approval labeling changes are a common and necessary part of approval maintenance, but the district court's approach would prevent reliance on even *new* data and information to support post-approval changes unless the trial conditions perfectly matched the labeling changes. This would be an impossible burden.

3. The District Court Would Undermine FDA's Use of Safety Data.

The district court found fault with FDA's reliance on data from the FDA Adverse Event Reporting System ("FAERS") because, after 15 years

of monitoring, FDA pared back the heightened reporting requirements it had previously imposed for mifepristone and brought them in line with those that apply to nearly every other approved drug. The district court objected to FDA's decision to no longer require reporting of some adverse events, for which it previously had imposed a heightened reporting requirement. Based on reports received over a 15-year period, the Agency determined that *extra* reporting was no longer needed, and that the reporting requirements should be equalized to those of "every NDA holder." FDA, New Drug Application No. 020687/S-020, Medical Review at 8 (Mar. 29, 2016); *see* 21 C.F.R. § 314.80(c)(1)(i). The district court further objected to FDA's reliance on the reporting that it did deem necessary. *See* Op. 38–39. But both of those actions were entirely reasonable exercises of FDA's authority and expertise, especially in light of the Agency's long experience with the drug in question. The district court's reasoning would require FDA to either blind itself to this critical source of safety data or impose an egregiously overinclusive reporting standard on drug sponsors. Either would impose unnecessary costs on industry and undermine the very purpose of FAERS reporting, which is to require reporting on issues of specific concern.

4. The District Court Adopted an Improperly Narrow Interpretation of "Serious and 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; *cf.* 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." Under the district court's view, FDA would be precluded from considering serious complications or negative experiences associated with a disease or condition in determining whether it is covered by that language. Op. 40–41; *id.* at 44. 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 practice and the industry research, development, and investment that relies on those practices.

Moreover, the district court did not need to interpret "meaningful therapeutic benefit" or "serious or life-threatening illness" at all. For more than 15 years, mifepristone has been regulated under 21 U.S.C. § 355-1, which does not include those limitations and 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 will have serious negative implications for other programs under the FDCA.

III. The District Court's Transformation of FDCA Requirements Will Chill Drug Development and Investment.

In all the ways discussed above and more, regulatory flexibility and respect for FDA's scientific judgment are crucial to fostering development of new and innovative drugs. 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 groundless approach, it is unlikely that a single one would have been approved—or that their approvals would have gone unchallenged—and countless patients would have suffered needlessly.

For example, if the district court's unworkable standard 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 risk a district court reversal of FDA's approval, 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. 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 a head-to-head study requirement. And, with the 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 these programs, delaying their availability to patients or even discouraging their development altogether.

In these ways and others, the district court's decision will shatter FDA's "gold standard" of review. Drug development is an increasingly high risk and high cost endeavor, with only a small fraction of drugs progressing from preclinical studies through clinical trials to market. The stability of FDA's regulatory framework provides much-needed assurance to investors that fund the development of lifesaving medications. This is particularly important in early development, when drug developers must secure sufficient capital to fund expensive clinical trials. By calling into question the Agency's longstanding framework for demonstrating safety and effectiveness, the district court's opinion destabilizes 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.

If allowed to take effect, the district court's decision will 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 the pharmaceutical industry.

CONCLUSION

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

Respectfully submitted,

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CERTIFICATE OF SERVICE

I certify that on April 11, 2023, the foregoing Brief of Pharmaceutical Companies, Executives, and Investors as *Amici Curiae* in support of appellants' motion for stay pending appeal 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 contains 4,542 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: April 11, 2023

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