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In the
Supreme Court of the United States

U.S. FOOD & DRUG ADMINISTRATION, *et al.*,

Applicants,

DANCO LABORATORIES, L.L.C.,

Applicant,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, *et al.*,

Respondents.

To the Honorable Samuel A. Alito, Jr., Associate Justice of the Supreme Court of the United States and Circuit Justice for the Fifth Circuit, on Applications to Stay Preliminary Injunction Issued by the United States District Court for the Northern District of Texas

MOTION FOR LEAVE TO FILE BRIEF AND BRIEF OF PHARMACEUTICAL COMPANIES, EXECUTIVES, AND INVESTORS AS *AMICI CURIAE* IN SUPPORT OF APPLICANTS

Laura Harris
Lauren Devendorf*
KING & SPALDING LLP
1185 Avenue of the Americas, 34th Fl.
New York, NY 10036

Anne M. Voigts
KING & SPALDING LLP
601 South California Avenue, Ste. 100
Palo Alto, CA 94034

**Admission pending in the State of New York; practice directly supervised by principals of the firm*

Eva A. Temkin
Counsel of Record
Paul Alessio Mezzina
Jessica Greenbaum
Joshua N. Mitchell
KING & SPALDING LLP
1700 Pennsylvania Avenue NW
Washington, DC 20006
(202) 737-0500
etemkin@kslaw.com

Counsel for Amici Curiae

April 14, 2023

MOTION FOR LEAVE TO FILE *AMICUS* BRIEF

Proposed *amici curiae* listed in the attached appendix request leave to file the attached brief in support of the emergency applications requesting a stay of the district court's April 7, 2023 preliminary-injunction ruling.

Proposed *amici* are pharmaceutical companies and executives and pharmaceutical-industry associations and investors, all of whom are acutely interested in the issues at stake in this case. The district court's decision radically alters the new drug application ("NDA") process through which drug sponsors seek Food and Drug Administration approval of new pharmaceutical products for sale and marketing. And the refusal by a divided Fifth Circuit to stay that deeply flawed decision in its entirety pending appellate review threatens to throw that process into further chaos.

Proposed *amici* collectively hold hundreds of approved NDAs and anticipate filing many more for drugs currently in development. Because they are acutely familiar with the high costs associated with drug development and the need for regulatory clarity, certainty, and predictability in that arena, they are well situated to explain to this Court the district court's misunderstanding of the statutory and regulatory provisions governing drug approval; the substantial chilling effect its decision, if not stayed in its entirety, will have on drug development; and the widespread harm that will result to the industry and its investors, as well as to healthcare providers and their patients.

For the foregoing reasons, proposed *amici* respectfully request leave to file the attached brief.

Respectfully submitted,

Anne M. Voigts
KING & SPALDING LLP
601 South California Avenue
Ste. 100
Palo Alto, CA 94034

Laura Harris
Lauren Devendorf*
KING & SPALDING LLP
1185 Avenue of the Americas
34th Fl.
New York, NY 10036

**Admission pending in the State of New York; practice directly supervised by principals of the firm*

Eva A. Temkin
Counsel of Record
Paul Alessio Mezzina
Jessica Greenbaum
Joshua N. Mitchell
KING & SPALDING LLP
1700 Pennsylvania Avenue NW
Washington, DC 20006
(202) 737-0500
etemkin@kslaw.com

Counsel for Applicants

April 14, 2023

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INTEREST OF *AMICI CURIAE* [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. *Amici* collectively hold hundreds of approved New Drug Applications ("NDAs") and anticipate filing many more for drugs currently in development. They are deeply familiar with the high costs associated with drug development and the need for regulatory clarity, certainty, and stability around drug approval. And they are therefore well positioned to explain to this Court how the lower-court orders in this case will upend the drug approval process and have a substantial chilling effect on drug development.

SUMMARY OF ARGUMENT

Each year, pharmaceutical developers and investors devote billions of research-and-development dollars to creating new medications to treat diseases and improve 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 drug-approval oversight to the Food and Drug Administration ("FDA").

Neither the district court's decision nor the Fifth Circuit's refusal to stay that decision in its entirety can be reconciled with that longstanding statutory and regulatory framework. The courts below unreasonably second-guessed FDA's sound and reasonable scientific decisions and misapplied applicable legal requirements. In

[1] No counsel for any party authored this brief in whole or in part, and no person or entity other than *amici* and their counsel made a monetary contribution to its preparation or submission.

particular, they held that it is likely arbitrary and capricious for FDA to (1) approve a drug or modify approved drug labeling without first requiring a clinical trial under conditions that perfectly match the labeling (including evaluating any changes in combination with each other); and (2) update adverse-event reporting requirements for a drug, after many years of intensive monitoring, yet still rely on relevant adverse event information to support labeling changes. *See* CA5 Op. at 33–35 (R.183-2).

If this Court does not stay the district court's order in its entirety pending full appellate review, it will 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 one drug, the logic of the decisions below could upend FDA's drug-approval process and empower any plaintiff to challenge the approval of other drugs, regardless of how long the drug has been on the market, on spurious 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.[2]

[2] Although the Fifth Circuit's opinion does not adopt every one of the district court's holdings, it perpetuates several of the district court's most egregious errors. This brief focuses on the holdings that pose the greatest threat to drug development, but does not address all of the lower courts' erroneous holdings.

Accordingly, *amici* urge this Court to stay the district court's order in its entirety pending full appellate review.

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 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 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.).

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 promulgated regulations that set 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.

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. As part of that program, it performs rigorous scientific studies and analyses to demonstrate the drug's safety and efficacy and develop physician labeling, including laboratory testing; preclinical (animal) testing; three separate phases of clinical studies averaging several thousand patients; and development of chemistry, manufacturing, and controls information. 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 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). 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).

That determination turns on a congressionally mandated benefit-risk calculation. Because all drugs have the potential for adverse effects, demonstrating a drug's safety does not require that a sponsor show that there are 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.

Adverse event reporting. FDA regulations require all NDA holders to review adverse drug experience information received from any source. 21 C.F.R. § 314.80(b). NDA holders must report within fifteen days all "serious and unexpected" adverse drug experiences. Unless already identified in the drug's labeling, these include deaths, life-threatening adverse drug experiences, inpatient hospitalization or

prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. *Id.* § 314.80(a). They also cover important medical events that, based on appropriate medical judgment, may jeopardize the patient or may require medical or surgical intervention to prevent the foregoing outcomes. *Id.* All other adverse drug experiences, with minor exceptions, are reported on a periodic basis. *Id.* § 314.80(c)(2) (quarterly for the first three years post-approval and annually thereafter).

C. FDA's drug-approval process 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 are particularly important for drug development, which presents considerable expense and business risk, for incentivizing investment in such development, and for patients.[3]

[3] 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 at 2 (Apr. 2021), *available at* https://www.cbo.gov/publication/57126.

ARGUMENT

I. The decisions below misapprehend the drug-approval framework Congress established and will upend drug development and patient access.

The district court ruled that all of FDA's actions regarding mifepristone dating back to its 2000 approval were likely unlawful. And while the Fifth Circuit found that plaintiffs' challenges to FDA's pre-2016 actions were likely time-barred, it agreed with the district court that the agency's actions since 2016—including approving labeling updates and removing various regulatory barriers to access—were likely arbitrary and capricious in violation of the Administrative Procedure Act ("APA").

In reaching those conclusions, both courts below substituted their own idiosyncratic views of clinical benefit and safety for the legislatively required, gold-standard benefit-risk analysis performed by FDA's medical and scientific professionals. In so doing, they 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 lower courts invented their own novel, unworkable standards to govern drug development and approval.

A. The courts below improperly substituted their own views for FDA's expert scientific judgment.

The decisions below represent 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 unelected 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)).

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 showed safe and effective use of mifepristone. In its place, the court relied on personal stories told by plaintiffs and cherry-picked, unreliable publications (including anonymous blog posts), 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. The Fifth Circuit, while not reaching the propriety of mifepristone's approval in 2000 nor endorsing every aspect of the district court's reasoning, likewise second-guessed FDA's analysis of drug-safety issues without a hint of deference to FDA's scientific expertise.

This result is contrary to 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"). Left unchecked, the lower courts' non-expert, judicial second-guessing of FDA's scientific judgment regarding NDA approvability threatens to cause turmoil for the industry, those that invest in it, and most importantly, the patients who depend on it.

B. The decisions below would create impossibly rigid new standards for drug development and approval.

Not only did the courts below improperly refuse to defer to FDA's expert judgment, they also adopted novel and inexplicably inflexible requirements to govern the drug-approval process. Nothing in the FDCA mandates the rigid requirements the district court and the Fifth Circuit 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 of the hallmarks 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). That flexibility additionally reflects Congress's considered decision to trust in FDA's expertise in distinguishing robust and reliable data from colorful but clinically and statistically meaningless (and potentially even misleading) anecdotes—disaggregating signal from noise in the inputs it receives.

The lower courts' inflexible 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 could narrow eligibility for these programs, delay patient access to life-saving medications, and discourage

development of those medications 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 that in turn would come at the expense of patients, who would lose access to potentially lifesaving and life-improving treatments.[4]

1. The decisions below wrongly limit a drug's approved labeling to the precise conditions of use studied in clinical trials and require a specific, rigid comparative trial design for labeling changes.

The district court held that FDA had likely acted arbitrarily and capriciously by failing to match the conditions of use in mifepristone's FDA-approved labeling with those in the clinical trials supporting approval. *See* D. Ct. Op. 51, 57–58 (R.137). Even though the court acknowledged that no statute or regulation requires FDA to "match" the conditions of use in approved labeling to the conditions in the supporting clinical trials, *id.* at 50 n.48, 60, it nevertheless ruled that FDA had likely violated the APA by not "cogently explain[ing]" why it did not do exactly that, *id.* at 60 (quotation marks omitted). The district court also concluded that FDA acted arbitrarily and capriciously by failing to cite "studies" specifically comparing the safety of proposed labeling changes "against the then-current regimen." *Id.* at 59.

The Fifth Circuit largely endorsed this aspect of the district court's reasoning, holding that FDA's actions in and after 2016 were likely arbitrary and capricious because FDA "eliminated REMS safeguards based on studies that *included those very*

[4] The lower courts' reasoning would also make it more difficult for FDA to do away with potentially onerous restrictions that real-world experience has demonstrated are not necessary. And that means access to critical drugs will be more difficult than it should be.

safeguards." CA5 Op. 34. The Fifth Circuit then went even further, adding an amorphous new requirement that although FDA had "studied the safety consequences of" certain changes "in *isolation*," it was likely arbitrary and capricious for FDA to approve labeling changes without "studies that evaluated the safety-and-effectiveness consequences of [those changes] *as a whole*." *Id.* at 35. Like the district court, the Fifth Circuit did not ground this conclusion in any statutory or regulatory text; rather, it used the guise of deferential arbitrary-and-capricious review to "substitute its judgment" for that of the expert agency. *State Farm*, 524 F.3d at 43.[5]

Through this misuse of arbitrary-and-capricious review, the courts below effectively transformed the 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. That rule has no basis in law.[6] 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. Similarly, incremental improvements to approved drugs (including new indications) are often supported by multiple types of studies and data—there is no requirement that specific studies must be conducted that evaluate proposed changes "as a whole." CA5 Op. 35.

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[5] It is not clear whether the Fifth Circuit meant to adopt the plaintiffs' and the district court's argument that labeling changes are permissible only if the labeling perfectly matches the clinical trial conditions, or their related argument that a labeling change is permissible only if supported by a clinical trial that perfectly compares the pre- and post-change conditions, or both. The court cited no authority for either proposition, and none exists.

[6] The only "support" the district court mustered came from one university's Institutional Review Board glossary page—not any statute, regulation, or agency guidance. *See* D. Ct. Op. 49 & n.46. Not to be outdone, the Fifth Circuit cited nothing at all. *See* CA5 Op. 35.

The Fifth Circuit likened FDA's approval of a change in labeling without a clinical trial evaluating every change under the precise labeling conditions to an agency eliminating a seatbelt requirement "based only on existing data of how cars perform *with*" seatbelts. CA5 Op. 34. That facile analogy demonstrates a deep misunderstanding of how clinical trial procedure and FDA review actually work. Clinical trials, particularly randomized, controlled trials, are simply not intended to perfectly mirror actual use conditions, even for changes made to approved drugs. Rather, clinical trials are—and always have been—"largely separate from routine clinical practice" and "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 trial parameters evolve to reflect new knowledge. Clinical trials thus often have restrictive eligibility criteria and additional monitoring procedures beyond those that would (or should) apply in post-approval 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 criteria are not required or expected to carry over into the approved labeling.

The approach taken by the courts below would discard this longstanding practice and require FDA to justify each and every difference between the labeling and the trial conditions. It could encourage parties to challenge FDA's decisions, and courts to second-guess them, any time the agency does not require a precise match between labeling and trial conditions—which is essentially every time FDA approves a drug.

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—a common practice for cutting-edge technologies and drugs for rare diseases, among others.

Likewise, incremental improvements to approved drugs (including new indications and other post-approval labeling changes) are often supported by multiple types of data. Post-approval labeling changes are a common and necessary part of approval maintenance, but the lower courts' approach could prevent reliance on even new data and information to support post-approval changes unless the sponsor conducted a clinical trial the conditions of which 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. It could also freeze drug labeling in time, discourage sponsors from continuing to innovate on their existing products, and deprive patients of access to improved treatments.

2. The decisions below undermine FDA's ability to generate and rely on useful safety data.

The courts below also found fault with FDA's management of and 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. *See* D. Ct. Op. 38–39; CA5 Op. 35. Once again, neither court found that FDA violated any statutory or regulatory requirement regarding FAERS; only that its actions were (in the courts' 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.

The Fifth Circuit's caricatured description of an agency that "eliminate[s] a reporting requirement for a thing and then use[s] the resulting absence of data to support its decision," CA5 Op. 35, bears little resemblance to reality. What really happened is that after *fifteen years* of unusually intensive monitoring of mifepristone firmly established the drug's safety profile, FDA determined that *extra* reporting was no longer needed. It therefore pared back the heightened reporting requirements it had previously imposed and brought them in line with the baseline reporting requirements that apply to nearly every other approved drug. *See* FDA, New Drug Application No. 020687/S-020, Medical Review at 8 (Mar. 29, 2016); FDA, New Drug

Application No. 020687/S-020, REMS Modification Review (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 (requiring that "serious and unexpected" adverse events be reported within 15 days and all other adverse events be reported annually).

There is no legal basis whatsoever for the lower courts' suggestion that this action was unreasonable or that it rendered the post-2016 FAERS data unusable. Those courts' reasoning would require FDA to either impose unnecessary and overinclusive reporting requirements on drug sponsors, or else blind itself to this critical source of safety data. Either path would impose unnecessary costs on industry and undermine the very purpose of FAERS, which is to require reporting on issues of specific concern. This is yet another instance in which the lower courts misused arbitrary-and-capricious review, unmoored from any statutory or regulatory text, to substitute their judgment for that of the expert agency.[7]

[7] The district court devoted much space to plaintiffs' claims with respect to FDA's 2000 NDA approval, claims that would also have significant implications in particular for drugs for rare diseases, but that the Fifth Circuit found were likely time-barred, *see* CA5 Op. 34 n.5. In addition, consideration of FDA's Subpart H regulations is unnecessary given Congress's codification of those provisions. *See* 21 U.S.C. § 355-1.

Should the Court nonetheless find it necessary to consider these issues, *amici* note that no legal authority justifies the district court's novel restrictions on FDA's discretion and exercise of its scientific judgment, which would undermine settled FDA practice and the research, development, and investment that relies on those practices. First, whether a drug confers a meaningful therapeutic benefit to patients is a matter of scientific judgment that calls for the application of FDA's scientific expertise. There is no legal requirement that "meaningful therapeutic benefit" be demonstrated by any particular type of study, or by a particular comparison with alternatives. Second, both evaluation of a drug's comparative benefit and assessment of whether a drug is intended to treat a "serious" or "life-threatening" disease or condition are important for several FDCA programs used to expedite FDA's review, all of which are vital for drug developers. *See* 21 U.S.C. § 356(a); *see also* 21 U.S.C. § 356(c) (accelerated approval); Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat.

II. The lower courts' 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 lower courts' approach, it is unlikely that a single one would have been approved—or that their approvals would have been unchallenged in court—and countless patients would have suffered needlessly.

For example, if the lower courts' 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 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 also ossify labeling, excluding new information gathered from outside the original clinical trials and threatening further innovations.

In these ways and others, the decisions below will 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 drugs candidates progressing from preclinical studies through clinical trials to market. The stability of FDA's

4491; *cf.* 21 C.F.R. § 314.500 (priority review designation). All of them would be rendered meaningless by the district court's requiring head-to-head clinical data and by its cramped interpretation of the terms "serious" and "life-threatening," and its artificial distinction between an "illness" and a "condition."

regulatory framework provides much-needed assurance to investors that 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, the opinions below threaten 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 lower court opinions 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 rigorous, well-established, and long-standing drug approval process, which is rooted in science and law.

CONCLUSION

The Court should grant applicants' request for a stay.

Respectfully submitted,

Laura Harris
Lauren Devendorf*
KING & SPALDING LLP
1185 Avenue of the Americas
34th Fl.
New York, NY 10036

Anne M. Voigts
KING & SPALDING LLP
601 South California Avenue
Ste. 100
Palo Alto, CA 94034

**Admission pending in the State of New York; practice directly supervised by principals of the firm*

Eva A. Temkin
Counsel of Record
Paul Alessio Mezzina
Jessica Greenbaum
Joshua N. Mitchell
KING & SPALDING LLP
1700 Pennsylvania Avenue NW
Washington, DC 20006
(202) 737-0500
etemkin@kslaw.com

Counsel for Amici Curiae

April 14, 2023

APPENDIX
OF PARTICIPATING *AMICI CURIAE*

Grace E. Colón, CEO, Board Member and Entrepreneur

Paul J. Hastings, CEO, Nkarta Inc.

Elizabeth Jeffords, CEO, Iolyx Therapeutics

RA Capital Management, LP (Peter Kolchinsky, Managing Partner)

Ram Aiyar, Biotech Executive

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

Patrick Amstutz, CEO, Molecular Partners AG

Ashvattha Therapeutics

Martin Babler, President and CEO, Alumis Inc.

Elizabeth Bailey, Managing Director, RH Capital

Rita Balice-Gordon, CEO, Muna Therapeutics

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

Nicholas Bayless, CTO, Centivax, Inc.

Jennifer Beachell, COO, Upstream Bio

Loren J. Beck, Chief Legal Officer, HDT Bio Corp.

C. Gordon Beck III, Founder and Managing Director, Princeton Biomedical Consulting LLC

Rishi Bedi, CEO, Y-Trap

Leonard Bell, MD, Principal Founder and Former CEO, Alexion Pharmaceuticals

Gregg Beloff, Managing Director, Danforth Advisors LLC

Jeremy Bender, CEO, Day One Biopharmaceuticals

Stephen Benoit, CEO, MDI Therapeutics

Heather Alisa Berger, Board Member and Investor

Kenneth A. Berlin, President and CEO, Ayala Pharmaceuticals

Gil Beyen, CEO, ERYTech Parham

Nailesh A. Bhatt, CEO, VGYAAN Pharmaceuticals

Biotechnology Innovation Organization

Remis Bistras, CEO, Diorasis Therapeutics

Sam Bjork, Partner, Digitalis Ventures

Blue Persimmon Group LLC

Paul Bolno, MD, President and CEO, Wave Life Sciences

Chris Bond, CSO, Notch Therapeutics

Jean Anne Booth, CEO, UnaliWear

Flavia Borellini, PhD, Retired Biotech Executive, Board Director

Daniel M. Bradbury, Executive Chairman, Equillium Inc.

Braidwell

Florian Brand, Co-Founder and CEO, atai Life Sciences

Amy Burroughs, President and CEO, Cleave Therapeutics

Cadence OTC

Abraham N. Ceesay, CEO

Celldex Therapeutics, Inc.

Cellevolve Bio Inc.

Melanie Cerullo, MS, CQA, Chief Quality and Regulatory Officer of a Biopharma Company

Gina S. Chapman, CEO, CARGO Therapeutics, Inc.

Sommer Chatwin, Partner, Braidwell

Jung E. Choi, Former Chief Business Officer, Global Blood Therapeutics

Bharatt Chowrira, PhD, JD, Biotech Executive

Scott Clarke, CEO, Ambagon Therapeutics

Jeffrey L. Cleland, PhD, Chairman, CEO, and President, Ashvattha Therapeutics

Kerry Clem, CCO

Ron Cohen, MD, President and CEO, Acorda Therapeutics, Inc.

Thomas A. Collet, PhD, President and CEO, Bilayer Therapeutics, Inc.

Viswa Colluru, PhD, Founder and CEO, Enveda Biosciences

Gerald E. Commissiong, President and CEO, Todos Medical, Ltd. and Todos Medical USA, Inc.

Emily Conley, PhD, CEO, Federation Bio, Board Member of Nuvalent, TMRW Lift Sciences, and Medrio

Lee Cooper, Lecturer, Thayer School of Engineering at Dartmouth College

Curae Pharma360 Inc.

Karim Dabbagh, President and CEO, Second Genome, Inc

Bassil Dahiyat, President and CEO, Xencor

Deep Track Capital

David de Graaf, PhD, President and CEO, Reverb Therapeutics, Executive Chairman, Ability Biologics

Steve Derby, CEO, General Ventures, Inc.

Lisa Deschamps, CEO, AviadoBio

Clarissa Desjardins, CEO, Congruence Therapeutics (a Canadian company)

Douglas Doerfler, Founder and CEO, MaxCyte, Inc.

Ken Drazan, CEO, ArsenalBio

Karen Drexler, Company Board Member

Doug Drysdale, CEO, Cybin

Eric Dube, PhD, President and CEO, Travere Therapeutics

Michael N. Dudley, PharmD, President and CEO, Qpex Biopharma

Barbara Duncan, Ovid Therapeutics, Board Director

Sandi Dunn, PhD, CEO, Phoenix Molecular Designs

Eric Easom, CEO, AN2 Therapeutics, Inc.

Jens Eckstein, PhD, Managing Partner, Apollo Health Ventures

Rami Elghandour, Chairman and CEO, Arcellx

John Ellithorpe, President

David M. Epstein, PhD, President and CEO, Black Diamond Therapeutics, Inc

Lavi Erisson, MD, CEO and President, Gensaic, Inc.

Jennifer Ernst, CEO, Tivic Health

EXXclaim Capital

EyePoint Pharmaceuticals

Andrew Farnum, CEO, Variant Bio

Eric A Floyd MS, MBA, PhD, Senior Vice President - Regulatory Affairs and Quality Assurance, Silence Therapeutics

Kristen Fortney, CEO and Board Member

Renee Gala, Biotech Executive and BOD Member

Scott Garland, Board Member, PACT Pharma

Dorothy Gemmell, President DKG Solutions, Inc.

Deborah Geraghty, PhD, CEO, Anokion

Gilead Sciences, Inc.

R. John Glasspool, CEO and President, Anthos Therapeutics Inc.

Corey Goodman, PhD, Managing Partner, venBio Partners

Anil K. Goyal, PhD, CEO and Co-Founder of a Biopharmaceutical Company and Co-Founder of OpenDoors Group

Adam Gridley, President and CEO, Allay Therapeutics

David-Alexandre Gros, MD, CEO, Eledon Pharmaceuticals

Sheila Gujrathi, MD, Biotech Executive, Entrepreneur, and Board Chair

Eric Haas, MEng, CEO, Ionic Cytometry Solutions.

Jay Hagan, CEO, Regulus Therapeutics

John Hallinan, Chief Development Officer, Danforth Advisors

Matthew Hammond, Principal, RA Capital Management, LP

Maurice T. Hampton, Biopharmaceutical CEO

Alex Harding, MD, Head of Business Development, CRISPR Therapeutics

Scott Harris, Chief Operating Officer, Cleave Therapeutics

Todd Harris, CEO, Tyra Biosciences

Kate Haviland, President and CEO, Blueprint Medicines

Mary Lynne Hedley, Sr. Fellow, Broad Institute of Harvard and MIT

Rekha Hemrajani, Biotech Executive and Board Member

Noreen Henig, MD, Chief Medical Officer, Kezar Life Sciences, Director (BoD), Avidity Biosciences

Jenny Herbach, CEO, Adventris Pharmaceuticals

Patrick Heron, Managing Partner, Frazier Life Sciences

Stephen Hill, COO

Arthur J. Hiller, CEO, Amasa Therapeutics, Inc.

Andrew Hirsch, President and CEO, C4 Therapeutics

Steven H. Holtzman, Chair, Camp4 Therapeutics

Reid Huber, PhD, Partner, Third Rock Ventures

Raquel Izumi, PhD, Chief Operations Officer, President and Founder, Vincerx Pharma

Elizabeth M. Jaffee, Deputy Director, Sidney Kimmel Cancer Center at Johns Hopkins, CSO, Adventris Pharmaceuticals

Freddy A. Jimenez, Esq., Senior Vice-President and General Counsel, Celldex Therapeutics, Inc.

Jeff Jonker, CEO, Belharra Therapeutics

Juvena Therapeutics

JeenJoo S. Kang, PhD, CEO, Appia Bio

Rosana Kapeller, MD, PhD, Biotech CEO and Board Member

Alex Karnal, CIO, Braidwell

Leen Kawas, Managing General Partner, Propel Bio Partners

Ciara Kennedy, CEO, Sorriso Pharmaceuticals

Stephen B. Kessler, CTO

Nikole Kimes, CEO, Siolta Therapeutics

Nina Kjellson, Biotech Investor, Public and Private Biotech Board Member, Healthcare Non-Profit Leader

Arthur Klausner, Executive Chairman, Concarlo Therapeutics

Jeffrey D. Klausner, MD, MPH, Clinical Professor of Medicine, Population, and Public Health Sciences, Keck School of Medicine of the University of Southern California

Jak Knowles, MD, CEO, Affini-T Therapeutics

Walter H. Koch, PhD

Joseph Kolchinsky, CEO

Peter Kolchinsky, Managing Partner, RA Capital Management, LP

Daphne Koller, Founder and CEO, insitro

John Kollins, Biopharmaceutical Company CEO and Board Member

Gautam Kollu, CEO and President, D2G Oncology

Adam Kolom, CEO, Related Sciences

Joanne Dove Kotz, CEO, Jnana Therapeutics

Brian Kreiter, CEO, Braidwell

Julie Krop, Chief Medical Officer, PureTech Health

Jane Lapon, Purpose Therapeutics Inc.

Mark Lappe, Chairman and CEO, Inhibrx

Donna LaVoie, LaVoieHealthScience

Russ Lebovitz, MD, PhD, CEO, Amprion Inc

Jonathan Leff, Partner, Deerfield Management

Dr. Jeremy M. Levin, Chairman and CEO, Ovid Therapeutics

Jonathan Lewis, MD, PhD, Chairman, Dugri, Inc.

Stanley Lewis, MD, MPH, Founder and CEO, A28 Therapeutics

Charlene Liao, PhD, President and CEO, Immune-Onc Therapeutics, Inc.

Ivana Liebisch, Biotech CEO and Board Member

Bob Linke, President and CEO

Dr. Yvonne Linney, Principal, Linney Bioconsulting

Uri Lopatin, MD, Biotech Executive and Board Member

Ted W. Love, MD, Former CEO, Global Blood Therapeutics

Rick Lundberg, President and CEO, Eikonizo Therapeutics, Inc.

Nancy Lurker, CEO, EyePoint Pharmaceuticals, Inc.

Macrogenics, Inc.

Nagesh K. Mahanthappa, PhD, MBA, Executive Chair, Exo Therapeutics

David Main, CEO, Notch Therapeutics

Hilary M. Malone PhD, CEO Biotech Neuroscience Company

Blake Mandell, CEO and Co-Founder, Transcend Therapeutics

Jeff Marrazzo, Co-Founder and Former Founding CEO, Spark Therapeutics

Bridget A. Martell MA, MD, President and CEO, Artizan Biosciences

Jon Martin

Sylvia McBrinn, Angel Investor, Former CEO, Axerion Therapeutics

Reenie McCarthy, CEO, Stealth BioTherapeutics

Sean McClain, Founder and CEO, Absci

Eileen McCullough, Serial Biotech Entrepreneur

Donnie McGrath, **MD, MPH**, Venture Partner, OrbiMed Advisors LLC

J. Andrew McKee, MD, CEO, Founder, and President, Headland Strategy Group, LLC

Medicines360

David Meeker MD, Chairman and CEO, Rhythm Pharmaceuticals

Darrin Miles, CEO and President, Nested Therapeutics

Jill C. Milne, PhD, CEO, Astria Therapeutics

Patrice M. Milos, PhD, Board Member, 54gene, SeqLL, Inc., ProThera Biologics and Vice President, Proof Diagnostics, Inc.

Emily Minkow, Biotech CEO

James Mitchell, MD, Chief Medical Officer, Veris Health, Radiation Oncologist, Bay Area Surgical Specialists

Nick Mordwinkin, CBO

Jodie Morrison, Biotech CEO and Board Member

John Mulligan, PhD, CEO, Bonum Therapeutics, Inc.

Genesio Murano, PhD, Expert, Biotechnology Reg Affairs

William J. Newell, CEO, Sutro Biopharma, Inc.

Nitrase Therapeutics, Inc.

Thomas J. Novak, CSO, Autobahn Labs

Peter Noymer, PhD, Life Sciences CEO and Board Member

Jessica O'Leary, Vice President Corporate Development of a Biopharma Company

Raul Oliva, CEO, Ergot Biosciences

Matt Ottmer, CEO, BioPharma Company

Julia Owens, CEO, Ananke Therapeutics

Michael Quigley, PhD, President and CEO, Therini Bio

Gerald E. Quirk, Chief Legal Officer, Syros Pharmaceuticals, Inc.

Rohan Palekar, CEO, 89bio Inc

Kevin Parker, PhD, CEO, Cartography Biosciences

Gisela A. Paulsen, MPharm, Former President and COO, Oncocyte Corporation, Entrepreneur-In-Residence, DigitalDX

Bernard Peperstraete, MD, Co-Founder and CEO, Acuamark Diagnostics, Inc.

Pfizer Inc.

Derrell D. Porter, MD, Cellevolve Bio Inc.

Michael Raab, President and CEO, Ardelyx, Inc.

Stephen Rapundalo, PhD, President and CEO

Debanjan Ray, CEO, Synthekine

Jake Reder, PhD, CEO, Celdara Medical, LLC

RH Capital

Safia K. Rizvi, CEO, CILA Therapeutics

Wendye Robbins, MD, Red Tower Partners Advisory

Bryan Roberts, Partner, Venrock

Glenn Rockman, Managing Partner, Adjuvant Capital, L.P.

Holly Rockweiler, CEO, Madorra

Mark Rus, CEO, Delix Therapeutics

René Russo, PharmD

Camille Samuels, Partner, Venrock

James Sapirstein RPh, Chairman, President and CEO, First Wave BioPharma

George Scangos, PhD, CEO, Vir

Marco Scheller, Senior Vice President Clinical Operations, CareDx, Inc.

Eef Schimmelpennink, President and CEO, Lenz Therapeutics

Ryan Schubert, SVP

Carlos Schuler, PhD, CEO, InCarda Therapeutics

Second Genome, Inc.

Alicia Secor, President and CEO, Atalanta Therapeutics

Lynn Seely, MD, President and CEO, Lyell Immunopharma

Thomas Seoh, CEO, Kinexum

Rajeev Shah, Managing Partner, RA Capital Management, LP

Laura Shawver, CEO, Capstan Therapeutics

Jay M. Short, PhD, Chairman, CEO, Cofounder, BioAtla, Inc.

Joao Siffert, Biotech CEO

Dr. Rona Z. Silkiss, Silkiss Eye Surgery

Adam Simpson, CEO of a BioPharma Company

Nancy Simonian, CEO, Syros Pharmaceuticals

Jake Simson, Partner, RA Capital

Samantha Singer, CEO

Renato Skerlj, PhD, President and CEO, Expansion Therapeutics Inc.

Erika R. Smith, CEO, ReNetX Bio, Inc.

Geoffrey W. Smith, Managing Partner, Digitalis Ventures

Julie Anne Smith, CEO, Nuvig Therapeutics, Inc.

Maria Soloveychik, PhD, CEO, SyntheX

Paula Soteropoulos, Biopharm Executive, Board Chairman, Venture Partner

Marcio Souza, CEO and President, Praxis Precision Medicines

Peter Strumph, CEO, Parvus Therapeutics

Arthur Thomas Suckow, CEO, DTx Pharma

Shehnaaz Suliman, CEO, ReCode Therapeutics

Synlogic Inc.

Laura Tadvalkar, Managing Director, RA Capital Management

Nicolas Tilmans, CEO, Anagenex

Samantha S. Truex, CEO, Upstream Bio

Rick E. Winningham, CEO, Theravance Biopharma

James B. Trager, PhD, CSO, Nkarta Inc.

Aetna Wun Trombley, **PhD**, CEO

Heather Turner, CEO, Carmot Therapeutics, Inc.

Marina Udier, CEO, Nouscom AG

Alexis van Lingen, Head of Quality, Nkarta, Inc.

Ramani Varanasi, Biotech Executive

Chris Varma, PhD, Co-founder, Chairman, and CEO, Frontier Medicines Corporation

Katherine Vega Stultz

Gregory Verdine, Erving Professor of Chemistry Emeritus, Harvard University and Harvard Medical School, Chairman, President and CEO, FOG Pharmaceuticals, Inc., President and CEO, LifeMine Therapeutics, Inc., Member, Board of Directors, Wave Life Sciences, Inc. (NASDAQ: WVE)

Dominique Verhelle, PhD, MBA, Biotech CEO

Christopher A. Viehbacher, President and CEO, Biogen

Sharon J. Vosmek, CEO and Managing Partner, Astia

Amanda Wagner, CEO

Hong I. Wan, President and CEO, Tallac Therapeutics

Neil Warma, President and CEO, Genexine, Inc.

Scott M. Wasserman, CEO, Latigo Biotherapeutics, Inc.

Frank Watanabe, President and CEO, Arcutis Biotherapeutics, Inc.

Wave Life Sciences

Yael Weiss, MD, PhD, CEO, Mahzi Therapeutics

Nancy Whiting, **PharmD**, CEO, Recludix Pharma

Fredrik Wiklund, Chief Executive Officer, Bright Peak Therapeutics

Matthias Will, MD

Leslie J. Williams, Co-Founder, President, and CEO, hC Bioscience, Inc.,

Katharine Yen, Biotech CEO

Angie You, CEO, Architect Therapeutics

Hanadie Yousef, **PhD**, Co-Founder and CEO, Juvena Therapeutics

Ashley Zehnder, CEO

Daphne Zohar, Founder and CEO, PureTech Health

Sandy Zweifach, Pelican Consulting Group, Inc.