Nos. 23-235 & 23-236

In the Supreme Court of the United States

U.S. FOOD & DRUG ADMINISTRATION, ET AL.,
Petitioners,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents.

DANCO LABORATORIES, L.L.C.,
Petitioner,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents.

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

BRIEF FOR FOOD AND DRUG LAW SCHOLARS AND PROFESSORS AS *AMICI CURIAE* SUPPORTING PETITIONERS AND REVERSAL

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January 30, 2024

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INTEREST OF THE *AMICI CURIAE*[1]

Amici curiae are U.S. food and drug law scholars and professors from academic institutions across the United States.[2] A full list of *amici* is included as an Appendix to this brief. *Amici* have expertise in food and drug law, including the drug approval process and regulation of pharmaceuticals under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq*. *Amici* submit this brief to address important issues raised by this case concerning the authority of the U.S. Food & Drug Administration (FDA or the Agency) to regulate prescription drugs.

SUMMARY OF ARGUMENT

The Federal Food, Drug, and Cosmetic Act sets out a comprehensive process under which FDA reviews and approves new drugs, and major changes to approved applications, before such products may be introduced into interstate commerce. FDA will approve a new drug application (NDA) only if it determines, based on the full record before the Agency, that the product is safe and effective for the

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

[2] The views expressed in this brief are those of the *amici* in their individual capacities and do not represent the views of their respective institutions.

proposed conditions of use. That determination requires the review of scientific evidence that sponsors[3] submit in support of their applications. In specified circumstances, the FDCA authorizes FDA to impose distribution and use restrictions to assure that a drug's benefits outweigh its risks, but the statute requires the Agency to minimize the burdens of such restrictions on patient access and, to the extent practicable, the healthcare system.

Ever since FDA approved mifepristone in 2000, it has been on the market with distribution and use restrictions, first through a regulatory pathway known as Subpart H and later through a statutory process known as a Risk Evaluation and Mitigation Strategy (REMS). In 2016, after more than 15 years of experience with the approved use of mifepristone, FDA concluded that some of the REMS restrictions should be eliminated or modified and that the approved conditions of use should be amended. In 2021, FDA determined that further changes to the use and distribution restrictions were warranted. These FDA actions were well-documented, science-based, and consistent with the statute's mandate to minimize burdens on patients and the health care delivery system.

The Fifth Circuit's ruling rests on critical misunderstandings of federal food and drug law, the regulatory history of mifepristone, and the evidence relied on by FDA. Contrary to the Fifth Circuit's conclusion, FDA had *far more* evidence than was

[3] In this brief, the term "sponsors" refers to marketing applicants and marketing application holders.

statutorily required to support the changes to mifepristone's labeled conditions of use and restrictions on use and distribution. Indeed, FDA regularly makes similar modifications with respect to other drugs based on far less evidence.

If allowed to stand, the Fifth Circuit's decision will destabilize the drug regulatory system established by Congress in the FDCA and implemented by FDA through regulations, guidance, and well-established practice. Affirmance by this Court is likely to have significant adverse effects on patients and pharmaceutical innovation.

ARGUMENT

I. Congress Has Granted FDA Broad Authority to Approve and Regulate Prescription Drugs.

Congress has established a comprehensive statutory process under which new drugs must be reviewed and approved by FDA before they may be lawfully introduced into interstate commerce. *See* 21 U.S.C. §§ 331(d), 355(a). Prior to marketing a new drug, a sponsor must file an NDA under section 505(b) of the FDCA. *Id.* § 355(b). Under section 505(d), FDA may not approve a drug if the NDA contains insufficient evidence to demonstrate safety or lacks substantial evidence of effectiveness. *Id.* § 355(d)(4), (5); *see also* 21 C.F.R. § 314.125(b). FDA's rigorous review and approval process includes not only a clinical assessment of the drug itself, but also, among other things, the "labeling proposed to be used for such drug." 21

U.S.C. § 355(b)(1)(vi).[4] These requirements set a high bar. Approximately 90% of drugs that enter clinical trials never make it to market. *See* Asher Mullard, *Parsing Clinical Success Rates*, Nature Reviews Drug Discovery (June 30, 2016), https://www.nature.com/articles/nrd.2016.137.pdf.

A sponsor seeking to change the conditions of use of a drug, such as adding or modifying an indication, revising the dosing regimen, or providing for a new route of administration, must submit and receive approval of a supplemental NDA (sNDA). *See* 21 U.S.C. § 505(b); 21 C.F.R. § 314.3(b). The safety and effectiveness standard applies equally to NDAs and to sNDAs seeking changes to the conditions of use. *See* 21 U.S.C. § 355(b), (d); *see generally* FDA, *Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, (May 1998), https://www.fda.gov/files/drugs/published/Providing-Clinical-Evidence-of-Effectiveness-for-Human-Drug-and-Biological-Products..pdf. The format, content, and review procedures for NDAs and sNDAs are identical in all relevant respects. *See, e.g.*, FDA, Ctr. For Drug Eval. & Rsch., *Policy and Procedures: NDAs/BLAs/Efficacy Supplements: Action Packages and Taking Regulatory Actions*, MAPP 6020.8, at 2 (June 13, 2016), https://www.fda.gov/media/72739/download.

In the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress amended the

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[4] Sponsors of generic drugs may file an abbreviated new drug application that relies on the safety and effectiveness data of an already-approved drug. *See* 21 U.S.C. § 355(j).

FDCA to grant FDA express authority to impose "risk evaluation and mitigation strategies" (REMS) on prescription drugs if necessary to address specific safety concerns. Pub. L. No. 110-85, § 901(b), 121 Stat. 823, 926–49 (2007) (codified at 21 U.S.C. § 355-1).[5] FDA may impose a REMS *only* if the Agency determines that a REMS is "*necessary* to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1(a)(1) (emphasis added). The components of a REMS may include, among other things, elements to assure safe use (ETASU), such as requirements that healthcare providers who prescribe the drug be certified or that the drug be dispensed to patients only in certain settings.

The FDCA, as amended, instructs FDA to use REMS with ETASU sparingly. They are appropriate only when necessary to ensure that the benefits of the drug outweigh the risks.[6] ETASU must be "part of [a] strategy to mitigate a specific serious risk listed in the labeling of the drug" and must be "commensurate" with this risk. 21 U.S.C. § 355-1(f)(1)(A), (f)(2)(A).

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[5] Prior to the passage of FDAAA, FDA had established a mechanism to impose distribution and use restrictions through regulation at 21 C.F.R. § 314.520, "Approval with restrictions to assure safe use." FDAAA codified and expanded that regulation by creating a statutory REMS framework.

[6] 21 U.S.C. § 355-1(f)(1)(A). Of the thousands of prescription drugs FDA has approved, currently there are only 64 REMS with ETASU. *See* FDA, *Risk Evaluation & Mitigation Strategy (REMS) Public Dashboard*, https://fis.fda.gov/sense/app/ca606d81-3f9b-4480-9e47-8a8649da6470/sheet/dfa2f0ce-4940-40ff-8d90-d01c19ca9c4d/state/analysis (last updated Jan. 29, 2024). Certain REMS are applicable to multiple applications. *See id.*

They must be designed "so as to minimize the burden on the health care delivery system." *Id.* § 355-1(f)(2)(D). And critically, the Act mandates that ETASU "not be unduly burdensome on patient access to the drug, considering in particular . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas) . . . and . . . patients with functional limitations." *Id.* § 355-1(f)(2)(C)(ii), (iii). In other words, ETASU must be the *least restrictive necessary* to ensure that the drug's benefits outweigh its risks.

II. The Fifth Circuit Applied Incorrect Legal Standards When Reviewing the 2016 REMS Modifications and Labeling Changes.

FDA follows a standard procedure when reviewing an NDA or an sNDA that includes proposed changes to a drug's prescribing information. First, FDA assembles an internal team of experts, including medical officers, safety officers, chemists, statisticians, and pharmacologists. Next, this team reviews the evidentiary record, which in recent years has often included only one controlled clinical study. *See* Robert M. Kaplan et al., *Review of Evidence Supporting 2022 US Food and Drug Administration Drug Approvals*, 6 JAMA Network Open e2327650, at 2 (Aug. 8, 2023), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2808057 (finding that in 2022, 65% percent of approvals of novel drugs, *i.e.*, drugs that had not been previously approved for any indication,

were supported by only one clinical study).[7] FDA will approve an application only if the Agency concludes that the record, including the clinical trial data and other confirmatory evidence, satisfies the statutory requirements for approval.

In May 2015, Danco Laboratories, LLC (Danco) submitted to FDA an sNDA with proposed changes to the prescribing information and REMS for mifepristone. J.A. 294.[8] Among other changes, Danco sought to increase mifepristone's gestational age limit to 70 days; revise the dosing regimen from 600 mg to 200 mg mifepristone, followed by misoprostol at a dose increased from 400 mcg to 800 mcg (administered buccally instead of orally); allow certain non-physicians to prescribe mifepristone; and eliminate the requirement for prescribers to report non-fatal adverse events.

For 10 months, FDA's experts combed through Danco's extensive evidentiary record in support of the proposed changes. They analyzed 54 unique studies

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[7] *See also* FDA, *Draft Guidance for Industry*, *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*, at 1–3 (Sept. 2023) (explaining that one "adequate and well-controlled clinical investigation" can be sufficient to warrant approval with other confirmatory evidence), https://www.fda.gov/media/172166/download.

[8] Most citations are cited to the Joint Appendix ("J.A."). When a document is not included in the J.A., we have cited to the Record on Appeal in the Fifth Circuit ("ROA").

(including 15 randomized controlled trials or equivalents), ROA 2287–2311;[9] 15 years of adverse event reporting and regulatory filings, including two in-depth REMS assessment reports, J.A. 306; 34 other articles and filings, J.A. 509–16; and three letters supporting the proposed changes from academic and professional organizations, including the American College of Obstetricians and Gynecologists, J.A. 441. These sources provided FDA's expert teams with an unusually extensive amount of data and information with which to evaluate Danco's proposal.

Although not required to do so by statute or regulation, FDA considered clinical trial data examining the "interrelated" impact of the sNDA's multiple changes, noting that "in some cases data from a given study were relied on to provide evidence to support multiple changes." J.A. 298. Notably, one randomized controlled trial and three observational studies closely mirrored the overall changes proposed in the sNDA. These studies evaluated "the exact proposed dosing regimen through 70 days gestation [and] . . . had a primary objective of evaluating medical abortion provision by non-physicians." ROA 2260. Based on these and other sources, FDA approved the sNDA in 2016, modifying both mifepristone's prescribing information and its REMS.

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[9] In addition to the 15 randomized controlled trials or equivalents, the 54 studies included interventional, observational, retrospective, and prospective trials, as well as systematic reviews and literature reviews of clinical studies.

As part of its approval, FDA published multiple review memoranda explaining the scientific rationale for its decision. FDA's explanation was meticulous and extensive, spanning close to 500 pages. *See generally,* FDA, *Mifeprex 2016 sNDA Review* (2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm. The memoranda demonstrate that the Agency comprehensively assessed the relative risk of adverse events when using the new dosing regimen of mifepristone in combination with misoprostol (the risk was low); evaluated whether the changes would negatively impact mifepristone's efficacy (they would not—the new dosing regimen was *more* effective); and analyzed whether the benefits of the drug would outweigh its risks under the modified REMS (they would).

Despite this unusually robust and well-documented record, the Fifth Circuit invalidated the approval because "[n]one of the studies [FDA] relied on examined the effect of implementing all of [the] changes together" and because the Agency failed to "explain" why it did not solicit such data. U.S. Pet. App. 53a. There is no legal support for a requirement that FDA either assess all proposed changes to a drug's REMS and labeled conditions of use in a single clinical study or justify why such a study is not necessary. FDA regularly approves multiple changes

without such data.[10] What the law *does* require is a REMS review that balances the drug's serious risks against the burdens on patient access imposed by any ETASU, and a comprehensive review of the drug's safety and effectiveness under the revised conditions of use. FDA easily met these standards in 2016.

A. The Fifth Circuit's "Cumulative Effect" Requirement Is Inconsistent with the FDCA's REMS Provision.

The Fifth Circuit's determination that FDA must "seek data on the cumulative effect" of multiple changes in a single study or expressly explain why it did not do so would add a new evidentiary requirement that does not appear in the statute or FDA's regulations. Such a requirement would seriously disrupt the statutory REMS framework by interfering with Congress's command to balance the specific risks of a drug against the burdens that restrictions on distribution or use would impose on patient access and on the healthcare delivery system. 21 U.S.C. § 355-1(f)(2). Furthermore, acceptance of the Fifth Circuit's approach would calcify unnecessarily burdensome restrictions, undermining the REMS framework that

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[10] *See, e.g.,* FDA, *BLA 125057/356 HUMIRA (adalimumab) Supplemental Approval* (2014), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125057Orig1s356ltr.pdf (simultaneously approving a new indication and a novel dosage form); FDA, *NDA 21880/S-034 Revlimid (lenalidomide) Supplemental Approval & REMS Modification Action* (2013), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/021880Orig1s034ltr.pdf (simultaneously approving a new indication and a new dosage strength).

Congress intended to be used narrowly and only where necessary to ensure that the benefits of a drug outweigh the risks.

i. The Statute Does Not Require Any Particular Type of Evidence to Impose, Modify, or Remove REMS Elements.

By Congress's direct instruction, REMS are not intended to be static. All REMS require sponsors to submit "assessments" at regular intervals, and FDA may require additional assessments at any time to evaluate whether to modify a REMS to ensure that the benefits of the drug outweigh the risks and to minimize associated burdens. 21 U.S.C. § 355-1(d), (g)(2)(B), (g)(2)(C). Moreover, a sponsor may voluntarily submit a REMS assessment and propose to modify the REMS at any time. *Id.* § 355-1(g)(1), (g)(4). Additionally, when a sponsor submits an sNDA seeking approval of a new indication for a drug subject to a REMS, it must include an assessment of the approved REMS with its application. *Id.* § 355-1(g)(2)(A). An assessment must include, "with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified." *Id.* § 355-1(g)(3). A request to modify a REMS must provide an "adequate rationale" to support the change. *Id.* § 355-1(g)(4)(A).

Although FDA did, in fact, examine numerous clinical trials when it approved the 2016 REMS modifications for mifepristone, the FDCA does not require

that *any* clinical trial data be included in a REMS assessment or provide the basis for a REMS modification. Congress could have chosen to require clinical investigations, as it has explicitly done in other contexts. *See* 21 U.S.C. § 355(d) (requiring "adequate and well-controlled investigations, including clinical investigations" to demonstrate a drug's effectiveness); *see also id*. § 355a(a) (defining "pediatric studies" to mean "at least one clinical investigation"); § 355(o)(3)(A) ("[FDA] may . . . require a responsible person for a drug to conduct a postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug"). It did not impose such a requirement for REMS assessments or modifications. Courts "presume differences in language . . . convey differences in meaning," *Henson v. Santander Consumer USA Inc.*, 582 U.S. 79, 86 (2017), and it is a "cardinal principle" of statutory interpretation that courts "must give effect, if possible, to every clause and word of a statute," *Loughrin v. United States*, 573 U.S. 351, 358 (2014) (cleaned up).

Through guidance and practice, FDA has put the FDCA's plain meaning into effect by not requiring clinical trial data for REMS assessments or modifications. In providing examples of acceptable sources of data to include in a REMS assessment, FDA does not even mention data from additional clinical trials. *See* FDA, *Draft Guidance for Industry, REMS Assessment: Planning and Reporting*, at 7–12 (Jan. 2019), https://www.fda.gov/media/119790/download. Instead, the Agency expects such assessments—and the resulting REMS modifications—to be based on "a combination of qualitative and quantitative information

about the REMS" derived from sources such as company databases, stakeholder surveys, drug utilization data, post-marketing adverse event data, observational data, epidemiological data, and "stakeholder outreach." *Id.* at 7–12. Such data are to be used both to assess the effectiveness of the REMS and "the impact of the program on the healthcare delivery system and on patient access to the drug." *Id.* at 12.

In practice, consistent with the FDCA, FDA regularly loosens REMS or releases them altogether without *any* clinical trial data at all. Since the establishment of the statutory REMS framework in 2007, FDA has fully removed 208 REMS—including ten REMS that contained ETASU at the time of their revocation.[11] In only one of these ten instances did FDA's public memoranda cite clinical trial data,[12] and in no instance did FDA cite a controlled clinical study comparing the safety of the drug without the ETASU against safety with the ETASU. Nor did FDA in any of these instances announce that it was reviewing the "cumulative effect" of the changes (or explain why it

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[11] *See* FDA, *Risk Evaluation & Mitigation Strategy (REMS) Public Dashboard*, https://fis.fda.gov/sense/app/ca606d81-3f9b-4480-9e47-8a8649da6470/sheet/dfa2f0ce-4940-40ff-8d90-d01c19ca9c4d/state/analysis (last updated Jan. 29, 2024).

[12] Even in this one case, clinical data was not submitted with the express purpose of modifying the REMS. Rather, data from an uncontrolled clinical trial was submitted to support the expansion of the approved indication to patients of all ages. Approving the expanded indication obviated the need for the ETASU that restricted distribution of the drug to patients 8 years or greater. *See* FDA, *REMS Modification Review*, at 308 (July 18, 2014), https://www.accessdata.fda.gov/drugsafda_docs/bla/2014/125291Orig1s136.pdf.

was not doing so), even when it removed multiple ETASU at once.

The flexible standards for REMS assessments and modifications are necessary to implement Congress's mandate that ETASU be maintained only when they are necessary to ensure a positive benefit-risk profile for the drug. The Fifth Circuit's approach of presumptively requiring sponsors to conduct expensive clinical trials to support REMS modifications would likely lead many sponsors to maintain unnecessary and overly burdensome REMS rather than undertake lengthy and costly clinical trials in an effort to modify them. ETASU would thus remain in effect even when the restrictions (1) are no longer necessary to ensure that the benefits of the drug outweigh the risks and (2) are imposing undue burdens on patient access or the healthcare system. In short, the Fifth Circuit's approach would ossify and burden drug regulation, harming the very patients that a REMS is intended to protect.

ii. FDA Had More Than Enough Data and Information to Modify the Mifepristone REMS in 2016.

Several of the 2016 changes—including allowing certain non-physician healthcare providers to prescribe and dispense mifepristone[13] and eliminating

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[13] Previously, only physicians could become certified prescribers, but advanced practice clinicians with state-law prescribing authority could prescribe "under the supervision of" a physician (...continued)

the requirement for prescribers to report non-fatal adverse events to Danco—were REMS modifications made under section 505-1. FDA "determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS." J.A. 285. In doing so, FDA considered evidence that far exceeded the "adequate rationale" statutory threshold.

For example, although Congress did not deem clinical trials to be necessary to support a REMS modification, Danco nonetheless provided data from over 3,200 women in randomized controlled trials and data from 596 women in prospective studies comparing medical abortion care by physicians versus nurses or nurse midwives. J.A. 497. These studies found *no statistically significant differences* in serious adverse events, ongoing pregnancy, or incomplete abortion (or in efficacy). *See id.*

FDA also had an ample evidentiary basis to support its determination that mandatory prescriber reporting of non-fatal adverse events was "not warranted." J.A. 392. Previously, certified prescribers had to sign an agreement indicating that they would report ongoing pregnancies, hospitalizations, transfusions, or other serious adverse events to Danco. In

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who was a certified prescriber. *See* FDA, *NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 Mg: Risk Evaluation and Mitigation Strategy (REMS)*, at 2 (2011), https://www.fda.gov/media/ 164648/download?attachment.

2016, the prescriber agreement form was amended to require such reporting only of fatal adverse events.[14]

FDA authorized this modification because "[t]he safety profile of Mifeprex [was] well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile [had] not changed over the period of surveillance." J.A. 317. Moreover, FDA explained that prescribers no longer needed to report non-fatal adverse event information to Danco because "[t]his information is being submitted to the Agency through other pathways including spontaneous adverse event reporting and the annual report." FDA, *REMS Modification Review*, at 10 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RiskR.pdf. In other words, FDA's standard adverse event reporting infrastructure, applicable to all FDA-approved drugs, was *already* capturing the non-fatal adverse events the heightened reporting requirements were designed to ascertain.[15] According to the Fifth Circuit, FDA's

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[14] Prescribers were never required to report such data to FDA. The Fifth Circuit's contrary statement, *see* U.S. Pet. App. 55a, is incorrect.

[15] For adverse drug experiences that are both serious and unexpected, FDA requires the NDA holder to submit a report to the Agency "as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant." 21 C.F.R. § 314.80(c)(1)(i). The applicant must then "promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports" and must submit follow-up reports to the Agency. *Id.* § 314.80(c)(1)(ii). FDA also has an extensive infrastructure for voluntary reporting, including by (...continued)

decision "failed to account for the fact" that the modifications to the conditions of use might "alter the risk profile" of the drug. U.S. Pet. App. 55a. But, in approving the sNDA, FDA concluded that these modifications would *not* meaningfully affect the risk profile. *See* U.S. Pet. 24.

Given the undeniable burdens to prescribers of heightened adverse event reporting, once FDA concluded that ongoing required reporting of non-fatal adverse events was not necessary to meet a specific risk, the FDCA *required* the Agency to amend the prescriber agreement accordingly. Even following the 2016 REMS revision, mifepristone remains subject to a more rigorous adverse event reporting regime than the vast majority of other drugs. The prescriber agreement continues to state that prescribers must report any patient deaths to the sponsor. Mifepristone and 34 other REMS drugs are currently the only medications sold in the United States for which prescribers or dispensers are required to report adverse drug experiences to the drug sponsor.

B. The Fifth Circuit's "Cumulative Effect" Requirement Is Inconsistent with the FDCA's sNDA Approval Standard.

FDA likewise reviewed an enormous amount of clinical data when it considered proposed changes to

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healthcare professionals and patients. *See* FDA, *Reporting Serious Problems to FDA* (May 18, 2023), https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda.

mifepristone's labeled conditions of use, including expansion of the approved indication to 70 days gestation and modifications to the approved dosing regimen (*i.e.*, decrease of mifepristone to 200 mg, increase of subsequent misoprostol to 800 mcg, and change of administration of misoprostol to buccal). In support of the dosing regimen modifications for mifepristone and misoprostol, FDA examined 22 different studies analyzing the effects of the proposed dosing regimen on over 35,000 women. J.A. 447. To change the indicated gestational age to 70 days, FDA relied on eight unique studies which enrolled more than 4,000 women. J.A. 453. Further, as previously noted, FDA reviewed multiple studies that closely mirrored the overall changes proposed in the sNDA. Together, this evidence was more than sufficient to satisfy the legal requirements for modifying mifepristone's prescribing information.

The FDCA sets forth the evidence that FDA must consider in assessing an sNDA that proposes changes to a drug's prescribing information (*e.g.*, the indication or dosing regimen). Although such changes are subject to a higher statutory standard than modifications to a REMS, the FDCA does not require FDA to evaluate all such proposed changes in a single clinical trial or explain why it did not seek such data.

Under section 505, FDA can approve an sNDA seeking changes to a drug's prescribing information only after determining that the drug, when used according to the new conditions of use, is both safe and effective. *See generally* 21 U.S.C. § 355(d). Effectiveness must be established by "substantial evidence," which is defined as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Id. § 355(d).

Because each drug and intended use presents its own specific effectiveness considerations, Congress charges the Agency with determining, on a drug-by-drug basis, what data are necessary to meet the "substantial evidence" standard. In 1997, Congress expressly confirmed FDA's longstanding flexible approach to determining if the "substantial evidence" standard has been met, amending the FDCA to codify FDA's discretion to rely on data from a single adequate and well-controlled clinical investigation along with confirmatory evidence from other sources.[16] The

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[16] Section 115(a) of the Food and Drug Administration Modernization Act of 1997 amended section 505(d) of the FDCA to state: "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence." Pub. L. No. 105-115, § 115, 111 Stat. 2296, 2313 (1997) (codified at 21 U.S.C. § 355(a)).

new language was intended to "guard against [a] rote requirement" for the data and evidence necessary to obtain marketing approval. *See* 143 Cong. Rec. S8163 (July 28, 1997) (statement of Sen. Jeffords). FDA has in many instances approved a drug or new use based on a single study with other confirmatory evidence.[17] The Fifth Circuit's requirement that FDA demand a clinical study examining the "cumulative effect" of all changes to support an sNDA is inconsistent with the evidentiary flexibility that FDA has exercised for decades under section 505(d)—flexibility that Congress expressly endorsed and codified.

The Fifth Circuit's imposition of a "rote requirement" also calls into question other aspects of FDA's flexible, drug-by-drug assessment practices. For example, FDA frequently approves drugs on the basis of clinical trials that were conducted under conditions different from those ultimately set forth in the approved labeling. In most cases, the conditions in the clinical trial are more restrictive than the subsequent FDA-approved prescribing information for the drug. This approach helps protect clinical study subjects, who are using the drug before FDA has determined it to be safe and effective. *See* J.A. 265 (2016 Citizen

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[17] *See* FDA, *Guidance for Industry, Providing Clinical Evidence of Effectiveness of Human Drugs and Biological Products* (May 1998), https://www.fda.gov/media/71655/download; *see also* Use of Advisory Committees by the Food and Drug Administration: Hearings Before the Subcomm. of the House Comm. on Gov't Operations, 93d Cong., 2d Sess. 122 (1975) (Statement of Peter Barton Hutt) (explaining that FDA has never treated a two-study standard as a "rigid requirement").

Petition Denial) (citing, as an example, biopsies conducted in clinical studies of menopausal hormone therapy that are neither recommended in the approved product labeling nor routinely performed by doctors when treating patients). FDA generally has recognized that traditional clinical trials are "largely separate from routine clinical practice" and are "designed to control variability and maximize data quality." *See* FDA, *Framework for FDA's Real-World Evidence Program*, at 5 (Dec. 2018), https://www.fda.gov/media/120060/download.

Moreover, based on reasonable clinical predictions, FDA frequently extrapolates the findings of a drug's pivotal trial to support approval for different indications and conditions of use than those used in the trial itself. *See* Daniel Feldman et al., *Use of Extrapolation in New Drug Approvals by the US Food and Drug Administration*, 5 JAMA Network Open e227958, (Apr. 19, 2022), https://jamanetwork.com/journals/jamanet workopen/fullarticle/2791292. Extrapolation can be vital to ensuring access to critical treatments for certain patient groups for whom it is either impractical or impossible to conduct meaningful and representative clinical studies. For example, FDA has interpreted the "substantial evidence" standard to allow for the approval of drugs designed to treat exposure to certain toxic biological, chemical, radiological, or nuclear substances based on extrapolation from animal studies. 21 C.F.R. § 314.600 *et seq*.; 64 Fed. Reg. 53960, 53964 (Oct. 5, 1999). Similarly—and as codified by Congress—FDA may rely on adequate and well-controlled studies in adults to approve certain drugs for pediatric use. *See* 21 U.S.C.

§ 355c(a)(2)(B) (allowing pediatric efficacy to be supported by efficacy data in adult trials with sufficient safety data). FDA may also extrapolate findings from female breast cancer studies to include male patients in FDA-approved indications, due to the lack of a sufficient number of male patients to include in clinical trials. *See* FDA, *Guidance for Industry, Male Breast Cancer: Developing Drugs for Treatment* (Aug. 2020), https://www.fda.gov/media/130061/download.

In short, the Fifth Circuit's approach is contrary to the standards Congress set for NDA and sNDA approval in section 505(d). If allowed to stand, it will undermine the Agency's ability to undertake the flexible, case-by-case assessment of each drug that is central to the regulatory system Congress designed.

III. FDA Had a Strong Basis to Determine that the In-Person Dispensing Requirement Should Be Removed.

In April 2021, FDA announced that it would not enforce the in-person dispensing requirement for mifepristone during the COVID-19 public health emergency if the other requirements of the REMS were met. *See* Janet Woodcock, FDA Acting Commissioner, FDA Letter to Am. Coll. of Obstetricians & Gynecologists and Soc'y for Maternal Fetal Med. (Apr. 12, 2021). In December 2021, FDA stated that the REMS must be modified to ease the burdens on patients and the healthcare system and directed Danco and the generic sponsor to initiate the process of modifying the REMS. J.A. 378, 407; *see* 21 U.S.C. § 355-

1(f)(2), (g)(4)(B).[18] In January 2023, FDA approved the sponsors' applications to remove the in-person dispensing requirement from the REMS while adding a new requirement for pharmacy certification. *See* FDA, *Risk Evaluation and Mitigation Strategy (REMS) Single Shared System for Mifepristone 200 mg* (Jan. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2023_01_03_REMS_Full.pdf.[19]

FDA's determination to eliminate the in-person dispensing ETASU was both lawful and well-supported. As discussed above, the FDCA requires sponsors to conduct regular "assessments" and to provide an "adequate rationale" to support REMS modifications. *See* Part II.A, *supra*. It does not require clinical data and mandates that ETASU not be unduly burdensome on patient access to the drug. FDA encourages the use of a flexible "combination of qualitative and quantitative information," including "postmarketing adverse event data." FDA, *Draft Guidance for Industry, REMS Assessment: Planning and Reporting*, at 7–12 (Jan. 2019), https://www.fda.gov/media/119790/download. Here, in addition to the assessment submitted by the drug

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[18] Following FDA's 2019 approval of a generic version of mifepristone, there are now two mifepristone sponsors: Danco and GenBioPro, Inc.

[19] Respondents have not challenged FDA's 2023 sNDA approval formally modifying the REMS to eliminate the in-person dispensing requirement, and the Fifth Circuit does not address the merits of that decision. We have thus focused our discussion here on FDA's 2021 announcement that it would require a REMS modification.

sponsors, FDA relied on the FDA Adverse Event Reporting System (FAERS) reports, safety information submitted to FDA during the public health emergency, published clinical data, and information provided by advocacy groups, individuals, and the respondents in separate ongoing litigation. J.A. 378–79.

The Fifth Circuit nevertheless held that FDA's determination was likely arbitrary and capricious because FDA "gave dispositive weight" to adverse event data in the FAERS database "despite the uncontested limitations of doing so," and because the "literature did not affirmatively support [FDA's] position." U.S. Pet. App. 59a, 61a. These conclusions are incorrect.

As an initial matter, FDA did not give "dispositive weight" to the data in the FAERS database. FDA also reviewed other sources of postmarketing safety data, including data published in the medical literature and data submitted by sponsors. J.A. 399. The Agency used these data to compare time periods when in-person dispensing was and was not enforced, concluding that "there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced." J.A. at 398; *see* J.A. 397-400.

Taken to its logical conclusion, the Fifth's Circuit's reasoning would preclude FDA from ever relying on the FAERS database (or other sources of adverse event data that are not 100% comprehensive), as "many adverse events will go unreported." U.S. Pet.

App. 60a. FDA routinely relies on the FAERS database and other postmarketing safety data to support a host of regulatory actions, including modifying or releasing REMS, updating a product's labeling information, communicating new safety information to the public, and even requesting that a company remove the product from the market.[20]

The Fifth Circuit also pointed to "significant limitations" of the published literature that FDA reviewed. U.S. Pet. App. 62a. It bears repeating that Congress did not require *any* clinical trials to modify a REMS under section 505-1 (21 U.S.C. § 355-1). Here, FDA considered clinical data from three studies evaluating retail pharmacy dispensing, three studies evaluating mail order dispensing, five studies evaluating clinic dispensing by mail, and one study evaluating clinic dispensing by courier, among others. J.A. 401–06.[21] FDA acknowledged limitations in the

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[20] *See, e.g.*, FDA, *Lotronex (alosetron hydrochloride) Information* (Sept. 8, 2023), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/lotronex-alosetron-hydrochloride-information (citing as support for removing the REMS that reporting of adverse events in FAERS "has been stable since 2002 and an increase in severe outcomes has not been observed"); Chisato Fukazawa et al., *Factors Influencing Regulatory Decision-Making in Signal Management: Analysis Based on the Signals Identified from the FAERS*, 55 Therapeutic Innovation & Regul. Sci. 685 (Mar. 2021) (analyzing regulatory actions taken based on signals FDA identified from FAERS, including labeling changes, REMS modifications, product recall, and withdrawal).

[21] When FDA initially announced that it would not enforce the in-person dispensing requirement during the COVID-19 public health emergency, it cited four of these studies. "The overall (...continued)

published studies, but concluded, based on its analysis of the totality of the information before it, that mifepristone would remain safe if the in-person dispensing requirement were removed. *See* J.A. 400. The published studies represented only one part of FDA's review. Even if, as the Fifth Circuit states, this literature alone "did not affirmatively support [FDA's] position," U.S. Pet. App. 61a, FDA's conclusion that the REMS should be modified was well-supported by these studies in combination with the extensive additional data and information in the regulatory record. Moreover, imposing a *de facto* clinical trial requirement would, as noted above, calcify burdensome and medically unnecessary REMS requirements.

As with its assessment of the 2016 REMS changes, the Fifth Circuit ignores key statutory requirements guiding FDA's review. Most notably, FDA considered the burdens imposed by the in-person dispensing requirement, a statutory directive the Fifth Circuit did not acknowledge. The in-person dispensing requirement prevented patients from meeting with providers remotely from their homes, thereby imposing on patients costs and logistical burdens associated with travel. *See* Greer Donley, *Medication Abortion Exceptionalism*, 107 Cornell L. Rev. 627,

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findings from these studies do not appear to show increases in serious safety concerns (such as hemorrhage, ectopic pregnancy, or surgical interventions) occurring with medical abortion as a result of modifying the in-person dispensing requirement during the COVID-19 pandemic." Janet Woodcock, FDA Acting Commissioner, FDA Letter to Am. Coll. Of Obstetricians & Gynecologists and Soc'y for Maternal Fetal Med., at 1–2 (Apr. 12, 2021).

648, 691 (Mar. 2022). It also forced prescribers to dispense mifepristone themselves instead of relying on pharmacies, creating logistical barriers associated with establishing and managing drug inventories. *See id.* at 645. The Agency concluded that "the REMS *must* be modified to remove the in-person dispensing requirement" so as to "render the REMS less burdensome to healthcare providers and patients." J.A. 407 (emphasis added). That determination was consistent with the statute and well-supported.

IV. Courts Should Be Reluctant to Overturn FDA's Well-Supported Scientific and Medical Determinations, Particularly Without the Full Administrative Record.

Regulating drugs is neither simple nor easy. Congress has chosen to delegate responsibility for determining whether drugs are safe and effective for an intended use to the trained experts at FDA. In upholding a stay, the Fifth Circuit substituted its non-expert judgment for the expert judgment of FDA. Moreover, the Fifth Circuit did so without the benefit of the complete administrative record, and thus without considering the full weight of the data on which FDA relied.

As this Court has recognized, Congress granted FDA primary authority over the determination of both a drug's safety and its effectiveness under Section 505(d) of the FDCA, 21 U.S.C. § 355(d), and the determination that a lack of evidence of safety or effectiveness merits withdrawal of an NDA or sNDA under Section 505(e), 21 U.S.C. § 355(e). *See Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 652

(1973) (stating that "Congress desired that the administrative agency" make the determination under Sections 505(d) and (e)). FDA's primary authority reflects the fact that the Agency has the scientific and medical expertise to make the complex determinations necessary to ascertain safety and effectiveness, including determinations regarding clinical trial design, dosing, and labeling. The benefit-risk analysis "inevitably involves a qualitative, subjective judgment by the Agency that weighs data and information about the drug's benefits and risks and considers uncertainties within a specific therapeutic and regulatory context." FDA, *Guidance for Industry, Benefit-Risk Assessment for New Drug and Biological Products*, at 19 (Oct. 2023), https://www.fda.gov/media/152544/download.

Here, the Fifth Circuit inappropriately rejected the extensive analysis and determinations of the FDA experts regarding the comparative benefits and risks of mifepristone and the safety measures necessary to ensure that the drug's benefits outweigh its risks

without unduly burdening access.[22] Moreover, the Fifth Circuit did so on the basis of only a "fraction" of the administrative record. Danco Brief at 36. In so ruling, the Fifth Circuit departed from the long-settled principle that a decision to overturn agency action requires a court to review "the full administrative record that was before the [agency] at the time [it] made [its] decision." *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 420 (1971), *abrogated on other grounds, Califano v. Sanders*, 430 U.S. 99 (1977); *see also Nat'l Res. Def. Council, Inc. v. Train*, 519 F.2d 287, 292 (D.C. Cir. 1975) (faulting judicial review of agency action on a "partial and truncated record"). Judicial review requires a court to have "neither more nor less information than did the agency when it made its decision." *Walter O. Boswell Mem'l Hosp. v. Heckler*, 749 F.2d 788, 792 (D.C. Cir. 1984).

In the District Court, all parties agreed that the court should defer ruling on Respondents' preliminary injunction request until FDA produced the complete

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[22] Members of this Court have recognized the importance of deferring to FDA's scientific determinations of drug safety and efficacy. *See, e.g.*, *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578, 579 (2021) (mem.) (Roberts, C.J., concurring) ("[C]ourts owe significant deference to the politically accountable entities with the 'background, competence, and expertise to assess public health'" (quoting *South Bay United Pentecostal Church v. Newsom*, 140 S. Ct. 1613, 1614 (2020) (mem.) (Roberts, C.J., concurring)); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 10, 12 (2020) (Alito, J., dissenting from denial of stay) (criticizing district court judge for "[taking] it upon himself to overrule the FDA on a question of drug safety," where district court enjoined FDA's in-person dispensation requirement for mifepristone during the COVID-19 pandemic).

administrative record. *See* ROA 3240–52; ROA 3588–95; ROA 3801–11. The District Court nevertheless ruled without waiting for the administrative record. The gaps in the record available to the courts below and this Court are striking: it includes only a small subset of the dozens of underlying studies FDA referenced in its 2016 Cross Discipline Team Leader Review.[23]

V. The Fifth Circuit's Ruling Undermines Public Health and Drug Development.

A decision to invalidate an approved drug application is a weighty matter. Indeed, when FDA itself proposes to withdraw an approved application, including an sNDA, Congress has directed that the Agency must carefully consider all the scientific evidence in accordance with a formal procedure. Specifically, FDA must provide notice and an opportunity for a hearing. 21 U.S.C. § 355(e); 21 C.F.R. §§ 314.150, 314.200(a)–(b). The sponsor must submit to the Agency the studies upon which it relies to justify a hearing, including all protocols and underlying raw data not already submitted in the application. *See* 21

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[23] The current record includes a tabular summary of the studies, but that is not a substitute for the studies themselves. *Compare* Cross Discipline Team Leader Review at ROA 2287 with, *e.g.*, ROA 464 (Maarit Mentula et al., *Immediate Adverse Events After Seconds Trimester Medical Termination of Pregnancy: Results of a Nationwide Registry Study*, 26 Hum. Reprod. 927 (2011)), ROA 726 (Beverly Winikoff et al., *Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age*, 120 Obstetrics & Gynecology 1070 (2012)), ROA 734 (Mary Gatter et al., *Efficacy and Safety of Medical Abortion Using Mifepristone and Buccal Misoprostol Through 63 Days*, 91 Contraception 269 (2015)).

C.F.R. § 314.200(d) (listing the kinds of data that can be submitted). Thereafter, FDA follows a rigorous process for conducting administrative proceedings, which may include a public evidentiary hearing, prior to withdrawing an approved drug application. 21 C.F.R. §§ 314.200(f)–(h), 314.201. These statutory and regulatory provisions enable FDA to remove unsafe or ineffective drugs from the market while protecting the rights of the application holder. *Cf. Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 639, n.2 (1973) (when implementing the procedures to withdraw an NDA approval, FDA "must not overlook both the interest of the public and the right of the proprietor in protecting the drugs that are useful in the prevention, control, or treatment of illness") (Powell, J., concurring).

Here, the problem with abrupt judicial intervention absent expert consideration of all scientific and medical evidence is clear: reverting to the pre-2016 mifepristone labeling as the Fifth Circuit envisions would reinstate a dose that FDA has determined (based on years of research and experience) is both *less effective* and *higher* than appropriate to optimally balance safety and effectiveness. More generally, the Fifth Circuit's ruling destabilizes the statutory and regulatory framework underpinning the approval of new drugs, with likely adverse consequences for pharmaceutical innovation and development.

A. The Fifth Circuit's Remedy Would Reinstate a Less Effective Dosing Regimen.

The Fifth Circuit's remedy—requiring Danco and the generic manufacturer to revert to the pre-2016 REMS and labeling—would have far-reaching implications. The Fifth Circuit brushes away concerns about these changes, stating that manufacturers will have "months of time needed to arrange for mifepristone to be distributed under the 2011 REMS." U.S. Pet. App. 67a. That explanation fails to consider the harmful effects of a labeling change for patients or broader consequences for the drug approval system.

Reverting to the pre-2016 labeling could harm patients by reinstating an approved dosing regimen that FDA found to be *less* effective. *See* J.A. 451 (stating that "the proposed new dosing regimen is *considerably more effective* for all gestations through 70 days, . . . especially when compared to the original data using the FDA-approved regimen" due to the lower incidence of "failures" (*e.g.*, incomplete abortions or medical complications such as heavy bleeding) caused by the prior dosing regimen) (emphasis added). According to FDA, the new dosing regimen results in "termination without any additional surgical intervention" between 91% and 98% of the time, compared to between 77% and 92% of the time for the pre-2016 dosing regimen. J.A. 450–51. As a result, under the 2016 label, fewer patients may need to seek additional care to complete their abortions.

A reversion to the pre-2016 labeling would remove dosing regimen changes proven to have a net positive

impact on patient safety, like the buccal administration of misoprostol. *See* Melissa J. Chen & Mitchell D. Creinin, *Mifepristone with Buccal Misoprostol for Medical Abortion: a Systematic Review*, Obstet. Gynecol. 13 (July 2015), https://escholarship.org/content/qt0v4749ss/qt0v4749 ss_noSplash_df9e086637dd3537850937bc146f0f2a.pd f?t=o02pbt (finding that buccal administration of misoprostol has slower absorption); Am. Coll. of Obstetricians & Gynecologists, *Practice Bulletin No. 143: Medical Management of First-Trimester Abortion* 123 Obstet. Gynecol. 149 (Mar. 2014) (noting that routes with rapid and significant absorption may have more adverse effects).

A return to the pre-2016 conditions of use would also triple the current labeled dosage of mifepristone, a step that would undermine years of testing to find the optimal minimum dose that balances safety and effectiveness. *See* J.A. 448–49 (identifying multiple prospective studies dating back to 2005 examining the proposed dosing regimen). As a policy matter, FDA considers it "advisable" to select the "lowest dose that will provide a desired therapeutic effect." FDA, Off. of Clinical Pharmacology, Div. of Pharmacometrics, *Request for Qualification of MCP-Mod as an Efficient Statistical Methodology for Model-Based Design and Analysis of Phase II Dose Finding Studies under Model Uncertainty*, at 10 (2015), https://www.fda.gov/media/99313/download. Doing so, FDA notes, can lower safety risks and "minimize unnecessary drug exposure that will not lead to additional benefit to the patient but may increase the risk or severity of adverse events." *Id*. The Fifth Circuit's approach is at odds with this principle.

Despite evidence that FDA's 2016 changes *increased* effectiveness and *improved* the safety profile of mifepristone, the Fifth Circuit concluded that the appropriate remedy was to reinstate the pre-2016 conditions of use. Based on FDA's alleged failure to consider the "cumulative effect" of the changes on mifepristone's safety profile, the Fifth Circuit would reinstate conditions of use that are less safe and less effective. That reasoning makes little sense.

B. The Fifth Circuit's Approach Would Have Significant Implications for the Drug Approval System.

Beyond the potential harm to patients taking mifepristone, the Fifth Circuit's ruling would have negative implications for the drug approval system. The Fifth Circuit's approach creates significant uncertainty by destabilizing long-held assumptions undergirding the stability of an approved NDA or sNDA. Pharmaceutical manufacturers engage with FDA on a range of complex issues related to drug review, approval, and labeling changes. Manufacturers are familiar with the FDCA and with FDA's regulations and procedures, and they make large investments in costly clinical trials and other research against the backdrop of that legal framework. If the clarity of the current regulatory system is clouded by a patchwork of judicial decisions regarding what is required for drug approval, future research and development could be chilled.

CONCLUSION

The Court should reverse the judgment of the court of appeals.

Respectfully submitted,

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APPENDIX

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APPENDIX A

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