No. 23-10362

IN THE UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

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

v.

U.S. FOOD & DRUG ADMINISTRATION; ROBERT M. CALIFF, Commissioner of Food and Drugs; JANET WOODCOCK, M.D., in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration; PATRIZIA CAVAZZONI, M.D., in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, Secretary, U.S. Department of Health and Human Services,
Defendants-Appellants

v.

DANCO LABORATORIES, L.L.C.,
Intervenor-Appellant

On Appeal from the United States District Court for the Northern District of Texas

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

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May 1, 2023

CERTIFICATE OF INTERESTED PERSONS

The undersigned counsel of record certifies that the following listed persons and entities as described in the fourth sentence of Fifth Circuit Rule 28.2.1 have an interest in the outcome of this case. These representations are made so that the judges of this Court may evaluate possible disqualification or recusal.

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3. American College of Pediatricians
4. Christian Medical & Dental Associations
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INTERESTS OF THE *AMICI CURIAE*[1]

Amici curiae are food and drug law scholars from academic institutions across the United States.[2] *Amici* are well known in their field, and many have deep expertise in the drug approval process. *Amici* submit this brief to address errors the district court made with respect to the U.S. Food & Drug Administration's authority to regulate prescription drugs. A full list of *amici* is included as an Appendix to this brief.

[1] This brief is submitted under Federal Rule of Appellate Procedure 29(a) with the consent of all parties. Undersigned counsel for *amici curiae* certify that this brief was not authored in whole or part by counsel for any of the parties, that no party or party's counsel contributed money for this brief, and that no one other than *amici* and their counsel have contributed money for this brief.

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

SUMMARY OF ARGUMENT

In the Federal Food, Drug, and Cosmetic Act (FDCA), Congress enacted a comprehensive process under which the Food and Drug Administration (FDA or the Agency) must review and approve new drugs before they may be introduced into interstate commerce. Before approving a drug, FDA is required to make a determination, based on the full record before the Agency, that a product is safe and effective for the proposed conditions of use. That determination requires the review of extensive scientific evidence that sponsors submit in support of drug marketing applications.

Pursuant to that statutory process, FDA approved mifepristone in 2000 after reviewing extensive data establishing the safety and effectiveness of the product. When approving mifepristone, FDA imposed certain restrictions on its distribution and use to address potential safety risks. FDA later modified these restrictions based on vast amounts of additional data generated during the drug's many years of widespread use. All of these actions were consistent with the FDCA as well as FDA's rules and policies.

Nevertheless, the district court brushed aside FDA's carefully considered decisions and issued an unprecedented order purporting to "stay" all approvals of mifepristone. The order rests on critical misunderstandings of federal food and drug law and the underlying regulatory history for mifepristone. The court below also

improperly replaced FDA's scientific and medical expertise with the court's own interpretations of the scientific evidence, upending the drug regulatory scheme established by Congress and implemented by FDA through regulations, guidance, and practice. This Court should reverse the district court's order.

ARGUMENT

I. Congress Has Vested FDA with the Authority to Approve and Regulate Prescription Drugs Based on Scientific Evidence of Safety and Effectiveness.

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). Since 1962, the general contours of the drug approval process have remained consistent. Prior to marketing a new drug, a sponsor must file a New Drug Application (NDA) pursuant to Section 505(b) of the FDCA. *See id.* § 355(b). The NDA must demonstrate that the drug is safe and effective for the proposed indication. *See id.* § 355(d). FDA's rigorous review and approval process encompasses not only a clinical assessment of the drug itself, but also, among other things, the "labeling proposed to be used for such drug." *Id.* § 355(b)(1)(vi). Pursuant to its statutory mandate, FDA must not approve a drug if the NDA contains insufficient information

to demonstrate safety or fails to demonstrate substantial evidence of effectiveness. *Id.* §§ 355(d)(4), (5); *see also* 21 C.F.R. § 314.125(b).[3]

In the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress granted FDA express authority to impose restrictions on the distribution and use of prescription drugs if necessary to address specific safety concerns, i.e., risk evaluation and mitigation strategies (REMS). *See* Pub. L. No. 110-85, § 901(b), 121 Stat. 823, 926-49 (2007) (codified at 21 U.S.C. § 355-1). 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." The FDAAA REMS framework codified and built on that regulation by creating a statutory REMS framework.

Under FDAAA, FDA may impose a REMS 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). The components of a REMS may include, among other things, elements to assure safe use (ETASU). ETASU are used if the drug has been shown effective, but FDA determines that the drug is associated with a specific serious risk and "can be approved only if . . . such elements are required as part of [a REMS] to mitigate a specific serious risk listed in the labeling of the drug." *Id.*

[3] Sponsors of generic drugs may file an Abbreviated New Drug Application (ANDA) that relies on the safety and effectiveness data of an already-approved drug. 21 U.S.C. § 355(j).

§ 355-1(f)(1)(A). In determining whether to require ETASU and, if so, what elements to include, FDA is required 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 health care delivery system. *Id.* § 355-1(f)(2).

While all prescription drugs are required to have prescribing information that informs health care professionals about the risks of the drug, FDA has required a REMS for only a small percentage of approved drugs. *See* FDA, *Risk Evaluation and Mitigation Strategies/REMS*, https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems (last updated Dec. 17, 2021). FDA has approved thousands of prescription drugs and currently there are only 61 REMS, of which 57 have ETASU. *See* FDA, *Risk Evaluation & Mitigation Strategy (REMS) Public Dashboard*, https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/risk-evaluation-and-mitigation-strategy-rems-public-dashboard (last updated Apr. 24, 2023).

II. FDA's Approval and Continued Regulation of Mifepristone Are Consistent with Federal Food and Drug Law.

A. FDA Adhered to Its New Drug Approval Standards in Approving the Original NDA for Mifepristone in 2000.

In September of 2000, after extensive scientific review, FDA approved mifepristone under Section 505 of the FDCA (21 U.S.C. § 355). FDA's determination that mifepristone was safe and effective under the statutory standards

for drug approval was based on a U.S. clinical trial and two French clinical trials, which collectively enrolled more than 2,500 patients. *See* ROA.591 (FDA Approval Memorandum). The district court's conclusions with respect to the 2000 approval are based on a fundamental misreading of the law and the regulatory record supporting the approval of mifepristone.

1. Mifepristone's Approval Was Not Expedited.

The district court incorrectly described the 2000 approval of mifepristone as an "accelerated approval" under FDA's Subpart H regulations. ROA.4309 (District Court Order). As a threshold matter, FDA's authority to approve mifepristone stems from Section 505 of the FDCA (21 U.S.C. § 355), not from the Subpart H regulations. Moreover, FDA's approval of mifepristone was not an "accelerated approval," which is a specific approval pathway based on different endpoints than FDA ordinarily requires.

In 1992, FDA promulgated the Subpart H regulations to address the approval, distribution, and use of drugs that were expected to provide meaningful benefits over existing treatments for patients with serious or life-threatening conditions. *See* 57 Fed. Reg. 58942, 58958 (Dec. 11, 1992) (creating 21 C.F.R. Part 314, Subpart H). Subpart H established specific regulatory mechanisms to facilitate approval of such drugs, but it did not alter the approval standard under Section 505 of the FDCA. To

use the Subpart H pathway, FDA still must find that there is substantial evidence of effectiveness and that the drug is safe for its intended use. *See* 21 U.S.C. § 355(d).

FDA approved mifepristone in accordance with the statutory standard for drug approvals in Section 505 of the FDCA. FDA also invoked Section 314.520 of its regulations, which provides for the imposition of conditions "needed to assure safe use" for certain drugs. 21 C.F.R. § 314.520(a). Although the district court characterized the approval of mifepristone as an "accelerated approval," FDA uses that term to refer to a separate provision of FDA's Subpart H regulations (21 C.F.R. § 314.510), which provides for the accelerated approval of a drug product based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. FDA did not invoke that provision in connection with the approval of mifepristone.

Nor was FDA's approval of mifepristone expedited as a practical matter. The mifepristone approval process took more than 54 months following NDA submission, far longer than the 18-month average for NDAs approved from 1996 through 2002. *See* U.S. Gov't Accountability Off. (GAO), GAO-08-751, *Approval and Oversight of the Drug Mifeprex* 27 (Aug. 2008), https://www.gao.gov/assets/gao-08-751.pdf. In 2008, GAO conducted an extensive audit of mifepristone's approval, concluding unequivocally that the approval was "consistent with the

approval processes" for other drugs approved with Subpart H restrictions on distribution and use. *Id.* at 6, 25.

Regardless of whether FDA properly invoked Section 314.520 to impose restrictions to assure safe use of mifepristone in 2000, any alleged procedural defect was rendered irrelevant by the subsequent transition of mifepristone's restrictions to a formal REMS after the passage of FDAAA. In FDAAA, Congress determined that drugs previously approved with elements to assure safe use under Section 314.520 were "deemed to have in effect" an approved REMS and required sponsors of such drugs to submit proposed REMS for approval by September 21, 2008. Pub. L. No. 110-85, § 909(b), 121 Stat. 823, 950-51 (2007).

When FDA reviewed its records to identify medications that would be deemed to have REMS under FDAAA, it identified 16 drugs—including mifepristone—that fell into that category. *See* 73 Fed. Reg. 16313, 16314 (Mar. 27, 2008). As part of the FDAAA transition, Danco submitted a supplemental NDA (sNDA) with a proposed REMS for mifepristone in 2008, and FDA approved a formal REMS with ETASU for mifepristone in 2011. *See* FDA, *Supplement Approval Letter for NDA 020687/S-014* at 1 (June 8, 2011), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020687s014ltr.pdf. FDA took this action in accordance with FDAAA and with FDA's established procedures to implement its REMS authorities.

2. Other Purported Deficiencies in FDA's Approval Decision Are Unfounded.

The district court also erred in its assessment of other aspects of FDA's review, approval, and labeling requirements as applied to mifepristone. Although we are unable to address each and every deficiency, we describe some of the most significant errors below.

First, the district court erroneously concluded that FDA's approval was arbitrary and capricious because the Agency did not mandate use of the transvaginal ultrasound that was part of the U.S. clinical trial protocol. ROA.4357 (District Court Order). There is no basis for such a "study match" requirement in the FDCA or FDA's regulations. Many clinical trials are conducted under conditions that are more restrictive than those set forth in the approved labeling, which is designed for post-approval clinical use. This approach helps protect clinical study subjects who, in many cases, use the study drug before FDA has made a determination that the drug is safe and effective. *See* ROA.662 (2016 Citizen 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). In other instances, clinical trials may employ stringent selection criteria to improve the power and practicality of a clinical trial. *See* FDA, *Good Review Practice: Clinical Review of Investigational New Drug Applications* 43 (Dec. 2013), https://www.fda.gov/media/87621/download. FDA

recognizes 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* 5 (Dec. 2018), https://www.fda.gov/media/120060/download.

Second, the district court incorrectly stated that FDA "entirely failed" to evaluate the "psychological effects" of mifepristone. ROA.4357 (District Court Order). The safety record for mifepristone that was before FDA as it considered whether to approve the marketing application for the drug included data about reported anxiety and depression in U.S. patients who were administered mifepristone. *See* FDA, *Medical Review for Application No. 20-687* at 12 (Nov. 22, 1999), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf (reporting that 2% of U.S. study participants reported anxiety); FDA, *Medical Officer's Summary of Safety Update for Application No. 20-687* at 2 (June 20, 1996), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P2.pdf (stating that of 28 U.S. patient reports of adverse experiences, one reported depression). Neither anxiety nor depression was a commonly reported adverse event.

Furthermore, the district court misunderstands FDA's role to the extent it implies that the mifepristone approval decision was flawed because the Agency failed to consider that a patient could regret her decision to choose mifepristone over

surgical abortion—or over proceeding with a pregnancy. Whether a particular drug is well-suited for a particular patient is generally a practice of medicine question that is outside FDA's purview. It is up to *prescribers*, not FDA, to offer their patients individually-tailored medical advice, taking into account each patient's individualized needs and goals.

B. FDA's Subsequent Actions With Respect to Mifepristone Were Lawful.

In 2011, FDA approved a REMS for mifepristone pursuant to its express statutory authority in Section 505-1 of the FDCA (21 U.S.C. § 355-1). Five years later, the Agency approved an sNDA containing modifications to the mifepristone REMS. Such REMS modifications are a standard part of the FDA REMS program, and the mifepristone modifications were supported by clinical evidence.

The district court concluded that FDA's 2016 REMS modification and subsequent decisions to lift the in-person dispensing requirement were arbitrary and capricious because: (1) FDA never reviewed a head-to-head clinical trial comparing the safety of the changes against the then-current regimen and (2) the elimination of the requirement for prescribers to report non-fatal adverse events left FDA with an incomplete picture of mifepristone's safety that compromised future Agency decisions. This analysis is flawed. First, the district court fundamentally misunderstood the statutory standards for modifying a REMS and misstated the data upon which FDA relied in approving the 2016 sNDA. Second, the district court

ignored the robust post-marketing adverse event reporting requirements applicable to all approved drugs (including mifepristone), as well as the unique, heightened adverse event reporting requirements still applicable to mifepristone under the REMS.[4]

1. FDA Had Adequate Basis to Modify the Mifepristone REMS.

The district court concluded that FDA arbitrarily and capriciously amended the REMS in 2016 without directly "comp[aring] the safety of the changes against the then-current regimen, nor under the labeled conditions of use." ROA.4365 (District Court Order). The text of the FDCA does not support this reading. The Act does not require FDA, when modifying or revoking a REMS, to assess data from such comparison studies or, for that matter, any particular type of data. Furthermore, reading the statute to require such clinical studies would have significant negative consequences to the public health.

Under the FDCA, FDA may modify a REMS either on the NDA holder's initiative or on its own initiative. *See* 21 U.S.C. § 355-1(g)(4). In the former situation, the NDA holder submits a proposed REMS modification to the Agency

[4] Any claims regarding FDA's 2021 enforcement discretion decision became moot when FDA revised the REMS for mifepristone in January 2023. Plaintiffs have not challenged FDA's 2023 sNDA approval, and the district court did not discuss it. Nevertheless, as described below, FDA's 2021 and 2023 actions were not arbitrary and capricious.

containing "an adequate rationale" for the modification. *Id.* § 355-1(g)(4)(A). In the latter situation, FDA may require the NDA holder to submit a proposed REMS modification if it makes certain determinations, including that a modification is necessary to ensure the benefits of the drug outweigh the risks of the drug or to minimize the burden on the health care delivery system. *See id.* § 355-1(g)(4)(B).

Although FDA in fact examined numerous controlled clinical trials when it approved the 2016 REMS modification, the text of the statute does not mandate *any* additional controlled clinical studies to support a REMS modification. The statute provides that FDA may order the NDA holder to perform an "assessment . . . to evaluate whether the approved strategy should be modified." *Id.* § 355-1(g)(2)(C). "Assessment" simply means "the action or an instance of making a judgment about something." *Assessment*, Merriam-Webster Dictionary, https://www.merriam-webster.com/dictionary/assessment (last accessed Apr. 30, 2023). It does not imply any particular method of analysis or level of evidence required for the review. By contrast, when Congress requires an FDA decision (such as the approval of a drug) to be based on clinical investigations, it is explicit on the point. *See* 21 U.S.C. § 355(d) (requiring "adequate and well-controlled investigations, including clinical investigations" to provide "substantial evidence" of effectiveness); *id.* § 355a(a) (defining "pediatric studies" to mean "at least one clinical investigation").

In providing examples of acceptable sources of data to include in a REMS assessment, FDA does not even mention data from additional clinical trials. FDA, *Draft Guidance for Industry, REMS Assessment: Planning and Reporting* 7-12 (Jan. 2019), https://www.fda.gov/media/119790/download. Instead, the Agency expects such assessments—and thus 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" to assess "the impact of the program on the healthcare delivery system and on patient access to the drug." *Id.* at 7-12.

Reading the REMS provisions of the FDCA to require FDA to obtain and review new clinical trial data before removing ETASU would frustrate Congress's purposes and goals in authorizing drug distribution and use restrictions. The FDCA does not encourage the liberal inclusion of ETASU in REMS; to the contrary, it cautions that potentially burdensome restrictions be used sparingly and only where necessary. The statute demands that ETASU be "necessary to assure safe use of the drug." 21 U.S.C. § 355-1(f)(1)(A). It requires these elements to be "commensurate" with a "specific serious risk listed in the labeling." *Id.* § 355-1(f)(2)(A). It compels FDA to publicly explain the need for the ETASU. *Id.* § 355-1(f)(2)(B). It requires the elements to 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). The district court did not even mention this statutory imperative.

Requiring the submission of new clinical trial data as a prerequisite to the modification or elimination of ETASU would keep stringent restrictions in place even after the Agency has acquired information demonstrating that they are no longer warranted in light of the statutory factors. Indeed, if the NDA holder were unable or unwilling to fund such studies, unduly burdensome restrictions could become permanent in direct contravention of Congress's statutory command.

FDA, with an eye toward reducing burdens and increasing access, typically loosens and releases REMS as they become less necessary due to the prescribing community's increasing knowledge about the drug and its experience using it. Since the establishment of the procedure in 2007, FDA has released 206 REMS—including eight REMS with ETASU. *See* FDA, *Risk Evaluation & Mitigation Strategy (REMS) Public Dashboard*, https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/risk-evaluation-and-mitigation-strategy-rems-public-dashboard. In none of these eight instances did FDA's decision rely on a

controlled clinical study comparing the safety of the drug without any ETASU in place against the then-current regimen.

Consider, for example, the REMS with ETASU for erythropoiesis-stimulating agents (ESAs) used to treat cancer, which required, among other things, a documented discussion between a certified prescriber and the patient about risks and benefits. FDA released this REMS after reviewing survey and utilization data contained in the sponsors' REMS assessments. *See* FDA, *Information on Erythropoiesis-Stimulating Agents (ESA) Epoetin Alfa (Marketed as Procrit, Epogen), Darbepoetin Alfa (Marketed as Aranesp)* (Mar. 31, 2017), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-erythropoiesis-stimulating-agents-esa-epoetin-alfa-marketed-procrit-epogen-darbepoetin. FDA explained that "[t]he results from surveyed prescribers demonstrate acceptable knowledge of the product risks" and "[t]he drug utilization data indicates appropriate prescribing of ESAs." *Id*.

Although the FDCA does not require the Agency to consider clinical studies when modifying a REMS, in approving the 2016 modifications to the mifepristone REMS, FDA relied on *dozens* of clinical trials demonstrating the drug was safe and effective when used and distributed pursuant to the revised conditions of use. As it did in 2000 for the initial approval, FDA assembled a team of experts to review all of the data submitted. *See Mifeprex (Mifepristone) Tablets Approval Package* (Mar.

29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm. The 2016 sNDA approval reflected careful deliberation by the Agency and a well-documented determination that the drug was safe and effective with the revised indication, labeling, and REMS. In 2018, the GAO reviewed the 2016 approval and, as it did in 2008 with respect to the 2000 NDA approval, concluded that FDA "followed its standard review process when it approved the [2016 sNDA]." GAO, GAO-18-292 *Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts* 1 (Mar. 2018), https://www.gao.gov/assets/gao-18-292.pdf.

In January 2023, FDA concluded yet another robust review of mifepristone, this time in response to an sNDA requesting modification to the REMS and corresponding labeling revisions. The review process itself was the same in all relevant respects as the process used in 2000 and 2016. *Mifeprex (Mifepristone) Tablets Approval Package* (Jan. 3, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/020687Orig1s025.pdf.

2. Mifepristone Continues to Be Subject to More Stringent Adverse Event Reporting Requirements than Almost Any Other Drug, and FDA Had Ample Basis to Remove the In-Person Dispensing Requirement.

According to the district court, FDA's elimination from the REMS of certain adverse event reporting requirements for prescribers resulted in "lax" reporting requirements and rendered FDA's 2021 enforcement discretion decision deficient.

See ROA.4363 (District Court Order) (discussing FDA's "lax reporting requirements"). The stay panel intimated that the 2023 sNDA approval was deficient for the same reason. *See* ROA.4412 (Stay Panel Order) (referring to FDA's decision as an "ostrich's-head-in-the-sand approach"). These statements by the courts do not take into account the stringent adverse event reporting requirements applicable to all drugs, including mifepristone, under FDA's regulations.

For adverse drug experiences that are both serious and unexpected, FDA requires "the applicant" (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." *Id.* § 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. *See id.* § 314.80(c)(1)(ii). This reporting obligation also applies to manufacturers, packers, or distributors that appear on the drug's label.[5] In addition, NDA holders must report all other adverse events (i.e., non-serious and/or expected) to FDA at regular intervals. *See id.* § 314.80(c)(2)(i). The same requirements apply to generic drugs approved under an ANDA. *See id.* § 314.98.

The district court also incorrectly discounted the fact that, even following the 2016 REMS revision, mifepristone remains subject to a more rigorous adverse event

[5] These entities can meet their obligation by submitting reports to the NDA-holder.

reporting regime than the vast majority of other drugs. In addition to the requirements that FDA's regulations impose on NDA holders, the mifepristone REMS requires *prescribers* to report to the manufacturer any deaths of patients who received the drug. Mifepristone is one of only a small number of drugs for which FDA requires *prescribers* to report adverse drug experiences. The Agency mandates prescriber reporting only as a part of REMS programs,[6] and only 25 REMS programs require prescribers to report adverse drug experiences. Not a single currently effective REMS requires prescribers to report all adverse drug experiences, as the mifepristone REMS did prior to 2016.[7]

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[6] Although FDA does not mandate healthcare professionals to report adverse events, it encourages them to do so. *See* FDA, *Reporting Serious Problems to FDA* (May 22, 2018), https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda.

[7] The stay panel suggested that FDA's decision to remove the requirement for prescribers to report nonfatal adverse events was particularly unreasonable because mifepristone's labeling includes a boxed warning and because the REMS includes a Patient Agreement Form that "prov[es] that emergency room care is statistically certain in hundreds of thousands of cases." ROA.4399 (Stay Panel Order). However hundreds of FDA-approved drugs have boxed warnings, *see* Christine M. Cheng et al., *Coverage of FDA Medication Boxed Warnings in Commonly Used Drug Information Resources*, 170 Arch. Intern. Med. 831 (2010), and none has a REMS requiring prescribers to report all adverse events. The serious adverse events highlighted in the mifepristone boxed warning are exceedingly rare. The mifepristone labeling provides that sepsis and hemorrhage rates are each 0.2% or less and that rates of transfusion and hospitalization related to medication abortion are each 0.7% or less. *Mifeprex (Mifepristone) Tablets Prescribing Information* 8 (Jan. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf. The stay panel's misreading of the Patient Agreement

In sum, mifepristone remains subject to *all* of the adverse reporting requirements in FDA's regulations, *as well as* the additional prescriber reporting requirements in the REMS. Therefore, contrary to the courts' comments, the 2016 modification of the adverse event reporting conditions of the REMS did not create a "lax" reporting scheme or deprive FDA of comprehensive post-marketing safety data.

Furthermore, FDA did not rely solely on the adverse event database when it decided to exercise enforcement discretion with respect to in-person dispensing during the COVID-19 public health emergency or when it subsequently revised the REMS to remove the in-person dispensing requirement. FDA's enforcement discretion decision—which is now moot as a result of the 2023 sNDA approval—was "the result of a thorough scientific review by experts," including a review of clinical outcomes data. ROA.807 (2021 FDA Response to 2019 Citizen Petition). And the sNDA approval relied on an extensive literature review, in addition to pharmacovigilance data and REMS assessment data submitted before and after the enforcement discretion decision went into effect. *See* FDA, *Review of Proposed Major REMS Modification* 19-36 (Jan. 3, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2023/020687Orig1s025SumR.pdf.

Form conflates the number of patients who require follow-up care with the much smaller number who seek emergency care.

III. The Remedies Adopted by the District Court Are Statutorily Improper and Would Undermine Drug Development and the Public Health.

A. A "Stay" Invalidating an Approval or Supplemental Approval Based on a Disagreement with FDA's Scientific Judgment Would Be Inconsistent with Statutory Requirements.

As discussed above, FDA has acted in accordance with the FDCA and its implementing regulations in making scientific determinations regarding mifepristone's safety and effectiveness. Yet, even if a court were to conclude otherwise, a "stay" of an approved application on the basis of a disagreement with FDA's safety and effectiveness determination is not an appropriate remedy. The FDCA and FDA's regulations dictate the procedures for withdrawal of an NDA. These procedures require *FDA* to find that certain statutory criteria apply and then to provide notice and an opportunity for an administrative hearing to the NDA holder. Both the district court's order (which purports to "stay" all mifepristone approvals) and the stay panel's order (which appears to "stay" all post-2016 approvals, including the ANDA for generic mifepristone) would conflict with FDA's statutory mandate and circumvent the provisions Congress and FDA have established to govern the withdrawal of an approved application.[8] *See* ROA.4373 (District Court Order); ROA.4419 (Stay Panel Order).

[8] To the extent that the stay panel's order allows mifepristone's 2000 NDA approval to stand and stays the 2019 ANDA approval, this outcome is inconsistent with the FDCA. Congress granted FDA the authority to approve generic drugs that rely on the safety and efficacy data of an already-approved drug (i.e., the reference listed

Under the FDCA, the Secretary of the U.S. Department of Health & Human Services is authorized to withdraw approval of an application if the Secretary determines that the evidence demonstrates that the drug's benefit-risk balance merits withdrawal. The Secretary has delegated the responsibility for making such a determination to the Commissioner of Food and Drugs (Commissioner). *See* FDA, *Staff Manual Guides 1410.10, Delegations of Authority to the Commissioner of Food and Drugs* 1.A(1) (Feb. 22, 2023), https://www.fda.gov/media/81983/download (delegating all functions vested in the Secretary under the FDCA to the Commissioner). Any potential withdrawal of an NDA or sNDA on safety or effectiveness grounds thus requires a finding by the *FDA Commissioner* that the evidence demonstrates that the drug's benefit-risk balance merits withdrawal. As the Supreme Court has recognized, Congress has granted FDA primary jurisdiction over both the determination of a drug's safety and effectiveness under Section 505(d) of the FDCA, 21 U.S.C. § 355(d), and the determination that there is a lack of such evidence meriting withdrawal under Section 505(e), 21 U.S.C. § 355(e). *See Weinberger v. Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609, 630 (1973) ("The

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drug (RLD)) upon a demonstration that the generic drug is the "same as" and bioequivalent to the RLD. 21 U.S.C. § 355(j)(2)(A). Plaintiffs do not argue that FDA erred in determining that the generic version of mifepristone is bioequivalent and pharmaceutically equivalent to the RLD. If the underlying RLD safety and effectiveness determination stands, then the ANDA approval should not be stayed. *Cf.* 21 C.F.R. § 314.161 (permitting an ANDA to refer to an RLD that was not withdrawn for safety or effectiveness reasons).

Act requires the Commissioner to disapprove any application when there is a lack of 'substantial evidence' that the applicant's drug is effective . . . Similarly, he may withdraw approval for any drug if he subsequently determines that there is a lack of such evidence."); *see also id.* at 633 ("The [FDCA] did not provide any mechanism other than the Commissioner's suspension authority under § 505(e), whereby an NDA once effective could cease to be effective."); *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)).

Moreover, under Section 505(e) of the FDCA, FDA may not withdraw an approved application unless it first provides "due notice and opportunity for hearing to the applicant." 21 U.S.C. § 355(e). FDA's regulations provide a specific set of procedures under which the Agency must provide notice of the opportunity for a hearing to the applicant and allow the applicant to submit data and information. *See* 21 C.F.R. §§ 314.150, 314.200. 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. Hynson*, 412 U.S. at 639, n.2 (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).

FDA has promulgated detailed regulations to implement its statutory authorities to withdraw existing approvals of FDA-regulated products. If a court were to determine that FDA acted arbitrarily and capriciously in approving, or maintaining the approval of, a prescription drug product, the appropriate remedy would be to mandate FDA to conduct an appropriate evidentiary hearing before the Commissioner or his designee to enable the Commissioner to make the findings required by the FDCA.

B. The District Court's Ruling Would Be Harmful to the Drug Approval System and Have Far-Reaching Consequences.

If this Court allows the district court's ruling to stand, there will be far-reaching implications for the entire drug approval system. No drug is without risk, and allowing a court to unilaterally overturn FDA's safety and effectiveness determinations could lead to challenges to the Agency's benefit-risk determinations for drugs it has approved to treat other diseases and conditions. Patients who rely on medications for their health and well-being could see their drugs removed from the market.

The potential for this outcome would also create widespread uncertainty in the pharmaceutical industry and chill research and development. FDA is the sole U.S. agency with which industry engages on issues related to drug review, approval, and labeling changes. Manufacturers are familiar with the FDCA and FDA's regulations and procedures, and they invest heavily in clinical research and costly

clinical trials against the backdrop of that framework. Manufacturers would be forced to simultaneously navigate a patchwork of judicial decisions regarding what is required for drug approval. Congress created a system for drug approvals and regulation, and courts should not circumvent it.

IV. FDA's Authority to Approve and Regulate Mifepristone is Not Limited by the Comstock Act.

FDA's approval and regulation of mifepristone is not limited by the Comstock Act, 18 U.S.C. §§ 1461, 1462, and the district court placed more weight on the Comstock Act than it can carry. When discussing FDA's actions, the district court ignored the many instances in which Congress affirmed FDA's authority to approve new drugs for introduction into interstate commerce and regulate their distribution, irrespective of the prohibitions in the Comstock Act.

When Congress enacted the FDCA in 1938, it authorized FDA to approve "*any* new drug" for "introduc[tion] into interstate commerce" and made no exception to this authority for abortifacients. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052 (1938) (creating 21 U.S.C. § 355(a)) (emphasis added). Courts frequently explain that the word "any" means "all" or "every." *See, e.g.*, *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1353 (2018); *Sullivan v. Stroop*, 496 U.S. 478, 486 (1990) (Blackmun, J., dissenting); *Regions Bank v. Legal Outsource PA*, 936 F.3d 1184, 1194 (11th Cir. 2019) ("[W]hen Congress uses

the word 'any' without 'language limiting the breadth of that word, "any" means all.'" (citation omitted)).[9]

Two prominent examples of drugs that FDA approved despite their inclusion in the Comstock Act at the time of approval are the oral contraceptive Enovid and mifepristone itself. In neither instance did Congress respond by limiting FDA's authority.

In 1960, FDA approved Enovid, the first oral contraceptive—despite the fact that contraceptives were Comstock-listed articles at the time, and despite the fact that the sale of contraceptives remained illegal in much of the nation.[10] *See* Martha Bailey, *"Momma's Got the Pill": How Anthony Comstock and Griswold v. Connecticut Shaped US Childbearing*, 100 Am. Econ. R. 98, 105-06 (2010). Just two years after Enovid's approval, Congress enacted the Kefauver-Harris Amendments to the FDCA. *See* Pub. L. No. 87-781, 76 Stat. 780 (1962). Rather

[9] When Congress amended the Comstock Act in 1971 to remove contraceptives from coverage under that Act, the House report noted that the FDCA would "still" (i.e., would continue to) regulate the "interstate *transportation* of drugs, medicines, and other articles for the prevention of conception." H.R. Rep. No. 91-1105, at 3 (1970) (emphasis added) (quoting the Department of Health, Education, and Welfare's conclusion); *id.* (quoting the Department of Labor's conclusion that the FDCA "would continue to apply to imports and shipments" of contraceptives). Congress thus confirmed its understanding that FDA regulates all drugs in interstate commerce, including Comstock-listed drugs.

[10] The Supreme Court had not yet decided *Griswold v. Connecticut*, 381 U.S. 479 (1965).

than curtail FDA's oversight and regulation of drug products, including with respect to contraceptives, the 1962 Kefauver-Harris Amendments strengthened FDA's authority to approve drugs for introduction into interstate commerce. And although a pending marketing application for an oral contraceptive was discussed during floor debate on the legislation, there was no suggestion that approval of the application would violate the Comstock Act or exceed FDA's authority. *See* 108 Cong. Rec. 21088 (Sept. 27, 1962). By December 1965—while contraceptives were still Comstock-listed articles—FDA had approved no fewer than seven oral contraceptives for introduction into interstate commerce. *See* FDA, *Fact Sheet: Oral Contraceptives* (Dec. 1965) (hereinafter FDA Contraceptive Fact Sheet).

Since FDA approved mifepristone in 2000, Congress has amended Section 505 of the FDCA (21 U.S.C. § 355)—which sets forth FDA's authority to approve and regulate new drugs—no fewer than 18 times, including post-*Dobbs*. It has also enacted the section authorizing REMS (21 U.S.C. § 355-1) and amended it seven times during this period, including post-*Dobbs*. Yet Congress has never amended the FDCA to curtail FDA's authority to approve abortifacients.[11]

[11] *See, e.g.*, Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002); Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (2003); Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003); Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007); Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010);

In sum, Congress has assigned FDA the task of ensuring that drugs submitted to it for approval are safe and effective for their intended use, including implementation of whatever restrictions FDA determines are necessary. The Comstock Act has no bearing on that decision. *See* 21 U.S.C. § 355(d) (listing grounds on which FDA may refuse to approve an application for a new drug); *see also* FDA Contraceptive Fact Sheet ("New drugs must be proved both *safe* and *effective* if used as directed, before clearance can be granted. But if the product *is* established as safe and effective, FDA *must* grant the clearance.") (emphasis in original)). By Congress's design, enforcement of the Comstock Act was not a factor in FDA's decision to approve or regulate mifepristone.

CONCLUSION

The district court's order should be reversed.

Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012); Consolidated Appropriations Act, Pub. L. No. 117-328, §§ 3001-3631 (2022) ("Food and Drug Omnibus Reform Act of 2022").

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CERTIFICATE OF SERVICE

I certify that on May 1, 2023, the foregoing document was served on all parties or their counsel of record through the CM/ECF system.

Dated: May 1, 2023

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CERTIFICATE OF COMPLIANCE

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