No. 23-2194

IN THE UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

GENBIOPRO, INC.,

Plaintiff-Appellant

v.

KRISTINA D. RAYNES, *in her official capacity as Prosecuting Attorney of Putnam County*, AND PATRICK MORRISEY, *in his official capacity as Attorney General of West Virginia*,

Defendants-Appellees

On Appeal from the United States District Court
for the Southern District of West Virginia (Huntington),
No. 3:23-cv-00058, Hon. Robert C. Chambers

BRIEF OF FOOD AND DRUG LAW AND HEALTH LAW SCHOLARS AS AMICI CURIAE IN SUPPORT OF PLAINTIFF-APPELLANT

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INTEREST OF THE *AMICI CURIAE*

Amici curiae are legal scholars from academic institutions across the United States, with expertise spanning U.S. food and drug law, health law, bioethics, and constitutional law.[1] Coming from a wide array of backgrounds, *amici* have published extensively and have been quoted widely on topics related to the U.S. Food and Drug Administration (FDA or the Agency) and its regulation of drugs used in medication abortion. *Amici* submit this brief to provide the Court with additional context on FDA's postmarket authorities under federal law, including limitations on the prescribing and use of mifepristone. A full list of *amici* is included as an Appendix to this brief.

STATEMENTS REQUIRED BY FED. R. APP. P. 29

All parties have consented to the filing of this brief. *Amici* certify that no party's counsel authored this brief in whole or in part, no party or party's counsel contributed money that was intended to fund preparing or submitting this brief, and no person other than *amici curiae* and their counsel contributed money that was intended to fund the preparation or submission of this brief.

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

SUMMARY OF ARGUMENT

In cases involving a preemption analysis, "the purpose of Congress is the ultimate touchstone" of the court's decision-making process. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (internal quotation and citation omitted). The district court concluded as an antecedent matter that it could not "find any evidence of Congressional intent in the [Federal Food, Drug, and Cosmetic Act (FDCA)] or [Food and Drug Administration Amendments Act of 2007 (FDAAA)] to preempt state laws of the type challenged here." JA266. This conclusion fails to appreciate the unique statutory and regulatory regime that applies to mifepristone and other drugs for which FDA has imposed a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU).[2]

Prior to the enactment of FDAAA, courts had held that FDA's statutory powers with respect to new drug approvals were limited to a binary determination of whether a drug met the relevant safety and effectiveness standards described in the FDCA. *See American Pharm. Ass'n v. Weinberger*, 377 F. Supp. 824, 827 n.10 (D.D.C. 1974), *aff'd*, 530 F.2d 1054. If FDA determined that a drug's benefits outweighed its risks, the drug could be approved and distributed nationwide. If FDA found that the risks of a drug were too great to justify the benefits, the

[2] This brief uses "mifepristone" to refer to both the branded and generic forms of this drug that are approved for the medical termination of intrauterine pregnancy.

Agency had limited tools to manage those risks, and the drug generally would not be approved for distribution in interstate commerce.

With the passage of FDAAA, Congress greatly expanded FDA's statutory powers, explicitly authorizing the Agency to require a REMS if it determines that such a program is necessary to ensure that the drug's benefits outweigh its risks. *See* 21 U.S.C. § 355-1(a). For a subset of REMS drugs—those with ETASU—Congress designed FDA's authority to reach even further. The REMS with ETASU regime newly authorized FDA to mandate use and distribution restrictions that dictate fundamental aspects of patient access, including who may prescribe the drug, where and how the drug can be dispensed to patients, and what testing and monitoring must be done in order for a patient to be treated with the drug. *See id.* § 355-1(f).

Congress's focus on patient safety as the basis for imposing postmarket access restrictions animates the statutory text and legislative history of the REMS with ETASU regime. Yet, there is another thread that motivated Congress to expand FDA's authority in this way. Congress recognized that the REMS with ETASU regime would allow more drugs to enter the national market, drugs that would not have been approved *but for* such elements being in place. *See* 21 U.S.C. § 355-1(f)(1)(A). In keeping with this goal, FDAAA mandated that any ETASU be crafted narrowly to address specific risks and must "not be unduly burdensome

on patient access to the drug." 21 U.S.C. § 355-1(f)(2). Thus, Congress intended for FDA to strike a precise balance: A REMS drug with ETASU must be subject to patient access restrictions that allow it to reach the national market in the first instance, but cannot be subject to restrictions that render obtaining the drug impracticable.

The breadth and depth of FDA's postmarket drug access authorities under the REMS with ETASU regime is well-illustrated in the regulatory history of mifepristone. The Agency has made a determination that mifepristone can be introduced to the national market only if it is subject to a comprehensive and detailed federal statutory and regulatory scheme that imposes special restrictions on access beyond what is required for the vast majority of prescription drugs.[3] Consistent with its statutory mandate, over the more than two decades since FDA first approved mifepristone, the Agency has determined that some of the REMS restrictions should be modified or eliminated to maintain the balance between safety and appropriate patient access. State legislation that interferes with patient access to the drug on the terms that FDA has set necessarily interferes with effectuating Congress's goals in establishing the REMS with ETASU regime.

[3] As discussed below, prior to enactment of FDAAA, FDA imposed postmarket restrictions through regulations in 21 C.F.R. Part 314, Subpart H. Since 2011, mifepristone has been subject to a REMS with ETASU. In 2019, the mifepristone REMS with ETASU became applicable to Plaintiff-Appellant's generic mifepristone product. In this brief, amici are not expressing any opinion on the scientific appropriateness of any version of the mifepristone REMS.

The district court acknowledges that Congressional intent must be determined in context. JA266 (citing *Medtronic*, 518 U.S. at 485). Yet the court's analysis does not take into account the exceptionality of the expanded authority that Congress granted to FDA in FDAAA. Nor does it adequately address the patient access considerations at the heart of the REMS with ETASU regime. For at least these reasons, the court's preemption analysis is flawed.

ARGUMENT

I. The REMS with ETASU Framework Under FDAAA Was a Significant Expansion of FDA's Postmarket Powers, Authorizing the Agency to Impose Comprehensive Postmarket Patient Access Restrictions.

The district court's discussion of Congress's intent behind the REMS with ETASU provisions ignores the larger statutory context and legislative history of FDAAA. Since 1938, section 505 of the FDCA has provided FDA with the authority to refuse to approve a drug on the basis of an inadequate demonstration of the drug's safety when used for its intended purpose. *See* 21 U.S.C. § 355(d). However, courts held that FDA was restricted to a binary yes or no decision with respect to the introduction of each drug into interstate commerce. *See American Pharm. Ass'n*, 377 F. Supp. at 829. FDAAA shifted the paradigm by granting the Agency a third option: to impose, as a condition for obtaining approval, postmarket use and distribution restrictions that establish the contours under which patients can access the drug. *See* 21 U.S.C. § 355-1(f). However, in granting these

authorities, Congress mandated that the REMS with ETASU regime minimize burdens on patient access. In so authorizing, Congress intended for FDA's postmarket use and distribution restrictions—which extended FDA's power to dictate prescribing, dispensing, and patient monitoring requirements—to establish both the floor and the ceiling for curtailing patient access to the approved drug in this very narrow context.

A. Prior to 2007, FDA Had Limited Options for Imposing Specific Patient Access Restrictions on Approved Drugs.

1. The 1938 Act and 1962 Kefauver-Harris Amendments

When Congress enacted the FDCA in 1938, it granted FDA the authority to oversee and regulate the introduction of food, drugs, medical devices, and cosmetics into interstate commerce. The FDCA established a comprehensive framework for FDA's pre-market review and approval of new drugs, requiring manufacturers to demonstrate that the drug was safe for its intended use and labeled with adequate directions for safe use. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052 (1938) (creating 21 U.S.C. § 355(a), (b)). In 1962, Congress enacted the Kefauver-Harris Amendments to the FDCA, strengthening FDA's pre-market approval authority over new drugs. For the first time, the statute expressly required manufacturers to show that new drugs were not only safe, but also effective for their intended use in order to obtain FDA

approval. Drug Amendments of 1962, Pub. L. No. 87-781, §§ 102, 104, 76 Stat. 780, 781, 784 (1962) (amending 21 U.S.C. § 355(a), (b)).

These broad FDA pre-market approval authorities remain today. Prior to marketing a new drug, a sponsor[4] must file a new drug application (NDA) under section 505(b) of the FDCA. 21 U.S.C. § 355(b). Under section 505(d), FDA must refuse to approve a drug if the NDA contains insufficient evidence to demonstrate safety or lacks substantial evidence of effectiveness under the proposed conditions of use. *See 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). 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. *See id.* § 355(j).

The FDCA arose out of a desire for national uniformity in the market for food and drugs. *See* Peter Barton Hutt et al., *Food and Drug Law: Cases and Materials* 429-30 (5th ed. 2022); Patricia J. Zettler et al., *Mifepristone, Preemption, and Public Health Federalism*, 9 J. L. & Biosciences 1, 19 (2022). Historically, industry supported early efforts to enact federal legislation, in part

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

because "inconsistencies in applicable state laws made operating on a national scale increasingly difficult." Ilyse D. Barkan, *Industry Invites Regulation: The Passage of the Pure Food and Drug Act of 1906*, 75 Am. J. Pub. Health 18, 20 (1985).[5]

Today, drug manufacturers make large investments in costly clinical trials and other research against the backdrop of a "promise of a national market being available to those manufacturers who do prove their drug safe and effective." Zettler et al., *Mifepristone, Preemption, and Public Health Federalism*, 9 J. L. & Biosciences at 19. The process for obtaining approval for a drug is onerous, time-consuming, and expensive. 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. Without the assurance of a national market upon approval, it would be more challenging to justify these investments, and future research and development could be chilled.

[5] The House Report accompanying the Pure Food and Drug Act of 1906, the predecessor to the FDCA, stated that "[o]ne of the hoped-for good results of a national law . . . is the bringing about of a uniformity of laws and regulations on the part of the States within their own several borders." H.R. Rep. No. 59-5056, at 8-9 (1906), *reprinted in* Hutt et al., at 429.

2. *American Pharmaceutical Association v. Weinberger* and Voluntary Postmarket Use and Distribution Restrictions

Courts have long recognized FDA's primary authority over the determination of a drug's safety and effectiveness necessary for approval. *See Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 652 (1973) (stating that "Congress desired that the administrative agency" make the determination under Section 505(d)). This 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. But while the 1938 Act and 1962 Kefauver-Harris Amendments created the framework for FDA's *pre-approval* review, prior to 2007, Congress had not provided express authority for FDA to mandate restrictions on a drug's use or distribution *post-approval*, other than imposing prescription status on a drug. *See* Durham-Humphrey Amendment, Pub. L. No. 82-215, 65 Stat. 648, 648-49 (1952) (codified at 21 U.S.C. § 353(b)(1)).

FDA's efforts to prevent diversion of methadone illustrate the constraint of the Agency's previously limited postmarket authorities.[6] FDA initially approved methadone in the 1950s as safe for use as an analgesic and antitussive agent, as

[6] "Diversion" refers to the use of legal drugs for illegal purposes. *See* Ctrs. for Disease Control & Prevention, *Drug Diversion*, https://www.cdc.gov/injectionsafety/drugdiversion/index.html.

well as for short-term detoxification. Physicians subsequently began prescribing the drug off-label for long-term maintenance in patients addicted to narcotics without adequate consideration of the drug's own addictive properties. *See* Hutt et al., at 1066. In 1972, FDA finalized regulations that purported to address diversion and abuse by limiting distribution of methadone to direct shipments from manufacturers to approved maintenance treatment programs, approved hospital pharmacies, and, in limited cases, selected community pharmacies. *See* 37 Fed. Reg. 26790 (Dec. 15, 1972).

In *American Pharmaceutical Association v. Weinberger*, the U.S. District Court for the District of Columbia struck down these regulatory provisions, holding that they "exceed[ed] the limits of FDA's statutory authority insofar as [they] purport[ed] to restrict the channels of distribution." 377 F. Supp. 824, 827 (D.D.C. 1974), *aff'd*, 530 F.2d 1054 (D.C. Cir. 1976) (*per curiam*). The court reasoned that "FDA's discretion under the [FDCA's] NDA provisions is limited to either approving or denying NDA's and nowhere is FDA empowered to approve an NDA upon the condition that the drug be distributed only through specified channels." *Id.* at n.9.

Weinberger, however, did not foreclose *voluntary* use and distribution restrictions negotiated between manufacturers and FDA. In 1992, FDA promulgated regulations known as Subpart H, which govern the approval, use, and

distribution of certain drugs "studied for their safety and effectiveness in treating serious or life-threatening illnesses" that "provide meaningful therapeutic benefit to patients over existing treatments." 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 under section 505(b) of the FDCA (21 U.S.C. § 355), including the imposition of conditions "needed to assure safe use" for certain drugs. 21 C.F.R. § 314.520(a). Because the request for approval under Subpart H was voluntary on the part of the manufacturer, these mechanisms were not inconsistent with *Weinberger*. *See* Hutt et al., at 1070. Between 1992 and 2007, FDA approved a limited number of drugs under this restricted distribution provision of Subpart H—one of which was mifepristone. U.S. Gov't Accountability Off., *Approval and Oversight of the Drug Mifeprex*, GAO-08-751, at 10 (Aug. 2008), https://www.gao.gov/assets/gao-08-751.pdf.[7]

FDA also provided guidance to drug manufacturers about the voluntary development of what FDA then called "Risk Minimization Action Plans" or "RiskMAPs." These strategic safety programs used distribution restrictions, among other tools, to minimize a drug's risks while preserving its benefits. For

[7] A separate provision of Subpart H (21 C.F.R. § 314.510), which is still in use, provides for accelerated approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. FDA did not use that provision in connection with the approval of mifepristone.

example, under a RiskMAP, a sponsor could agree to the use of certification requirements for prescribers and pharmacies or requirements for patients to undergo lab testing to demonstrate safe use. *See* FDA, *Guidance for Industry, Development and Use of Risk Minimization Action Plans*, at 10 (Mar. 2005), https://www.fda.gov/media/71268/download.

3. Early Efforts to Address the Limits of FDA's Post-Approval Authorities to Regulate a Drug's Use and Distribution

Although sponsors could voluntarily accept and comply with postmarket use and distribution restrictions, the Agency lacked explicit authority to mandate and enforce such restrictions. The Executive Branch and Congress began exploring legislative expansion of FDA's toolkit to address this gap in the 1970s. In 1977, a Review Panel on Drug Regulation established by the Secretary of Health, Education, and Welfare issued a report concluding, among other things, that improvements were needed to increase FDA's authority in the post-marketing period. *See* S. Rep. No. 96-321, at 11 (1979). In response to the Panel's findings, the Senate Committee on Labor and Human Resources drafted the Drug Regulation Reform Act of 1979. *See* S. 1075, 96th Cong. (1979). The bill, which passed the Senate but not the House, sought to "give more flexible authority to the Food and Drug Administration to deal with problems that arise after drugs are on the market." S. Rep. No. 96-321, at 13 (1979).

According to the Senate Committee, the drug approval process failed to provide FDA with an adequate range of options. The Committee stated that, when a new drug was brought before FDA, the Agency effectively had only two options: "approve the drug for unrestricted, virtually permanent use" or "disapprove the drug." *Id.* at 38. In his testimony before the Senate in 1979, then FDA Commissioner Donald Kennedy noted that this statutory scheme had the potential to prevent "valuable drugs that could not be regarded as safe for general distribution" from being "available promptly" to those in greatest need. *Drug Regulation Reform Act of 1979: Hearing on S. 1075 Before the S. Comm. on Labor & Hum. Resources*, 96th Cong. 368 (1979) (statement of Donald Kennedy). To address this issue, the Drug Regulation Reform Act of 1979 would have given FDA a third option: to impose distribution, dispensing, and administration requirements at the time of drug approval. *See* S. 1075, 96th Cong. § 506 (1979) (proposing requirements including restricting the use of a drug to practitioners with specific training or experience and mandating patient monitoring procedures). Though the Drug Regulation Reform Act of 1979 failed, concerns regarding FDA's limited options persisted.

In 2006, FDA commissioned the Institute of Medicine (IOM) to write a report on drug safety. In its report, the IOM acknowledged that "FDA has some ability to ask for and negotiate with sponsors about various risk management and

other actions," but concluded that FDA "need[ed] new authority or a clarification of existing authority to apply restrictions and conditions on distribution." IOM Report at 167-68. The IOM recommended that Congress "ensure that [FDA] has the ability to *require* . . . postmarketing risk assessment and risk management programs as needed to monitor and ensure safe use" of drug products, with restrictions matching "the specific safety concerns and benefits presented by the drug product." *Id.* at 169 (emphasis added).

B. REMS Drugs with ETASU Are Uniquely Subject to Comprehensive—and Carefully Calibrated—Post-Approval Access Restrictions as a Condition of Approval.

In 2007, Congress passed FDAAA, which gave FDA express statutory authority to impose REMS on prescription drugs when needed to ensure that a drug's benefits outweigh its risks. Pub. L. No. 110-85, § 901(b), 121 Stat. 823, 926–49 (2007) (codified at 21 U.S.C. § 355-1).[8] REMS are designed to mandate behaviors and actions that support safe use of a drug. *See* FDA, Risk Evaluation and Mitigation Strategies: REMS (May 16, 2023), https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems. FDA considers whether additional communications to

[8] Consistent with Congress's intent to expand FDA's postmarket authorities, FDAAA also authorized FDA to require sponsors to conduct certain postmarketing studies and clinical trials and to amend a drug's labeling with new safety information. *See* Pub. L. No. 110-85, § 901(a), 121 Stat. 823, 922-26 (2007) (codified at 21 U.S.C. § 355(o)).

patients (e.g., medication guides, patient package inserts) and to health care providers (HCPs) (e.g., letters to HCPs) about the drug are necessary, as well as whether a particular packaging or disposal system is required, to mitigate a risk associated with the drug. *See* 21 U.S.C. § 355-1(e).

Beyond the requirements imposed under a baseline REMS, FDAAA also authorized FDA to add ETASU upon a determination that such elements are necessary to authorize the drug's entry into the nationwide market or to allow it to remain on the market. *See id.* § 355-1(f) ("Providing safe access for patients to drugs with known serious risks that would otherwise be unavailable"). Through the ETASU provisions, Congress explicitly authorized the imposition of limits on patient access to the drug, including: (1) who can prescribe the drug—e.g., threshold HCP qualifications and training requirements; (2) where patients can obtain the drug—e.g., requirements that pharmacies, practitioners, or health care settings that dispense the drug be specially certified, or requirements that the drug be dispensed only in certain health care settings, such as hospitals; and (3) under what conditions patients can obtain the drug—e.g., requirements that patients be subject to ongoing monitoring or laboratory testing as part of their treatment with the drug, and that patients and prescribers sign a patient-prescriber agreement before the drug is dispensed. *See id.* § 355-1(f)(3)(A)-(F).

Although the REMS with ETASU regime gave FDA important, express authorities to impose use and distribution restrictions, Congress also established limitations on this power. FDAAA mandates that FDA engage in a balancing exercise. Under section 505-1 of the FDCA, 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." *Id.* § 355-1(a)(1) (emphasis added). To incorporate ETASU into a REMS, FDA must determine that the drug "can be approved *only if*, or would be withdrawn unless, such elements are required . . . to mitigate a specific risk listed in the labeling of the drug." *Id.* § 355-1(f)(1)(A). In other words, ETASU must be the *least restrictive necessary* to ensure that the drug's benefits outweigh its risks. [9]

To determine whether ETASU are the least restrictive necessary, FDAAA directs FDA to consider the nationwide impact on access. Specifically, FDAAA

[9] Furthermore, 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). Consistent with the FDCA, FDA regularly loosens REMS or releases them altogether. Since 2007, FDA has fully removed 208 REMS—including ten REMS that contained ETASU at the time of their revocation. *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 Feb. 11, 2024). 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.

mandates that ETASU "not be unduly burdensome on patient access to the drug, considering in particular—(i) patients with serious or life-threatening diseases or conditions; (ii) patients who have difficulty accessing health care (such as patients in rural or medically underserved areas); and (iii) patients with functional limitations." *Id.* § 355-1(f)(2)(C). ETASU must also be designed "so as to minimize the burden on the health care delivery system," to the extent practicable. *Id.* § 355-1(f)(2)(D). This statutory text compels a sweeping consideration of patients subject to and impacted by the REMS with ETASU program, i.e., patients nationwide. Similarly, analysis of burden on "*the* health care delivery system," indicates an across-the-board, unified assessment, compelling FDA to assess burden on a national scale.

The statutory scheme governing REMS drugs with ETASU reflects Congress's intent to "find the optimal balance between competing policy goals," specifically between patient safety and access. Patricia J. Zettler, *Pharmaceutical Federalism*, 92 Ind. L.J. 845, 875 (2017). Congress understood that the REMS with ETASU regime would allow for *more* drugs to come to market. By granting FDA expanded authorities to mandate postmarket access conditions—and to establish the contours through which patients obtain the drug nationwide—Congress enabled FDA to approve drugs that otherwise would have been rejected or withdrawn. *See id.* § 355-1(f)(1)(A). The debates indicate that Congress saw

FDA's REMS authority—including its ETASU authority—as a means of expanding FDA's "toolbox" to enable faster approval and a greater ability to identify and address problems across the nation. *See* 153 Cong. Rec. S11937, S11939 (daily ed. Sept. 21, 2007) ("We gave [FDA] a toolbox, a whole bunch of different things that they can now do so that drugs will be approved faster, and then when that clinical trial that we call the whole population of the United States kicks in, there is a mechanism for following [use of the drug]"); 153 Cong. Rec. S5759, S5767 (daily ed. May 9, 2007) (statement of Sen. Enzi) ("Our goal is to get the drugs to the market quicker and to discover problems faster and get them corrected.").

By adding not only the REMS authority, but also the REMS with ETASU authority, to FDA's existing preapproval authorities under section 505, Congress enabled FDA to regulate a limited subset of drugs not only from initial clinical research until approval, but also through prescribing, dispensing, and use—allowing FDA to dictate patient access in a way that FDA is not authorized to do for other approved drugs. The district court failed to consider this critical context when it considered the preemptive effect of the FDAAA provisions.[10]

[10] The district court also places undue emphasis on uncodified language from the 1962 amendments to the FDCA preserving state authority except where "there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793. This savings clause expressly applied *only* to the 1962 amendments, and not to (continued…)

II. Mifepristone Has Been Subject to More Federal Oversight Than Perhaps Any Other Prescription Drug.

The regulatory history of mifepristone illustrates the scope and reach of FDA's authority to regulate REMS drugs with ETASU and to determine the terms on which the drug will be accessible to patients nationwide. For more than twenty years, FDA has tightly restricted who can prescribe mifepristone and where and how patients can obtain it.

In 2000, FDA approved an NDA for Mifeprex—the brand name for mifepristone, now distributed and marketed by Danco Laboratories, LLC ("Danco")—for the medical termination of intrauterine pregnancy through 49 days' gestation in combination with another drug, misoprostol. *See* FDA, *Approval Letter for NDA 20687*, at 1 (Sept. 28, 2000), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf. FDA invoked its Subpart H regulations to impose restrictions on the drug's use and distribution, and Danco agreed to these restrictions as a condition to approval. *See id.* at 2.

When Congress expressly authorized FDA to require a REMS by enacting FDAAA in 2007, Pub. L. No. 110-85, § 901(b), 121 Stat. 823, 926-49 (2007) (codified at 21 U.S.C. § 355-1), it declared that drugs previously approved with

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subsequent expansions of FDA's authority like FDAAA. *See* Zettler, *Pharmaceutical Federalism*, 92 Ind. L.J. at 868-69, n.159.

elements to assure safe use under Subpart H were "deemed to have in effect" an approved REMS, Pub. L. No. 110-85, § 909(b)(1)(A), *reprinted at* 21 U.S.C. § 331 note. When FDA reviewed its records to identify previously approved medications that would be deemed to have an approved REMS under FDAAA, it identified 16 drugs—including mifepristone. *See* 73 Fed. Reg. 16313, 16314 (Mar. 27, 2008). Congress was well aware that the "deemed to have in effect" language would sweep mifepristone into this new statutory scheme. Indeed, on the Senate floor, two Senators discussed the fact that, pursuant to the text of FDAAA, mifepristone would be distributed under a deemed REMS. *See* 153 Cong. Rec. S5759, 5765 (daily ed. May 9, 2007); 153 Cong. Rec. S5444, 5469 (daily ed. May 2, 2007).[11]

Pursuant to FDAAA and FDA's procedures to implement its REMS authority, Danco submitted a supplemental NDA (sNDA) with a proposed REMS for mifepristone in 2008, and FDA approved a mifepristone REMS with ETASU in 2011. *See* FDA, *Supplement Approval Letter for NDA 020687*, at 1 (June 8, 2011),

[11] During the Senate mark-up, one Senator endorsed an amendment that would have suspended FDA's approval of mifepristone, but it was rejected. *GOP Fails to Narrow Scope of FDA Reform Bill During Senate Mark-Up*, Inside Washington's FDA Week (Apr. 20, 2007), https://www.jstor.org/stable/e26714182. The engrossed Senate bill required the mifepristone manufacturer to submit a proposed REMS to FDA for approval on a more accelerated schedule than that applicable to manufacturers of other drugs. *See* S. 1082, 110th Cong., 1st Sess., tit. II, § 214(b)(3)(B) (engrossed in Senate, May 9, 2007). However, the bill as enacted treated all drugs "deemed to have in effect" an approved REMS alike, requiring manufacturers to submit proposed REMS for approval by September 21, 2008. Pub. L. No. 110-85, § 909(b).

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020687s014ltr.pdf.

Among other elements, the ETASU in the original mifepristone REMS sharply restricted where patients could obtain mifepristone and who could prescribe the drug. Unlike typical approved drugs that can be prescribed by licensed healthcare providers, picked up at pharmacies, and taken at home, FDA mandated that the drug regimen be administered in a clinic, medical office, or hospital (i.e., a health care facility) by or under the supervision of a physician who met certain qualifications and was certified under the mifepristone REMS. *See* FDA, *Risk Evaluation and Mitigation Strategy (REMS) for NDA 20687*, at 1-2, 5 (June 8, 2011), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2011-06-08_Full.pdf. This not only meant that patients could not take the medication at home, but also that the types of providers who could administer mifepristone were substantially restricted. Among other things, the provider needed to be a physician who was able to "assess the duration of pregnancy accurately," "diagnose ectopic pregnancies," "provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide

such care through others," and "assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary." *Id*. at 7. [12]

The original mifepristone REMS also imposed unique, heightened adverse event reporting requirements. Certified prescribers had to sign an agreement indicating that they would report ongoing pregnancies, hospitalizations, transfusions, or other serious adverse events to Danco. *See id.* Such reporting requirements existed on top of the stringent adverse event reporting requirements applicable to all drugs, including mifepristone, under FDA's regulations. *See* 21 C.F.R. §§ 314.80, 314.98. These regulations require all sponsors to submit reports to FDA within 15 calendar days of receiving information about serious and unexpected adverse drug experiences, to "promptly investigate," and to submit follow-up reports to the Agency. *Id.* § 314.80(c)(1); *id.* § 314.98 (applying the same requirements to generic drugs approved under an ANDA).

Since 2011, consistent with its statutory mandate to balance specific risks of a drug against the burdens of a REMS on patient access and the healthcare delivery

[12] The ETASU largely tracked the restrictions originally imposed under Subpart H. As scholars have noted, these restrictions went beyond what FDA requires for most non-controlled substances. *See* David S. Cohen et al., *Abortion Pills*, 76 Stan. L. Rev. __ (forthcoming 2024) (draft at 19), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4335735 (discussing FDA's use of the restricted distribution provision in Subpart H as the Agency "regulat[ing] mifepristone *more* harshly than the vast majority of drugs, not more leniently or more expediently" (emphasis added)); Greer Donley, *Medication Abortion Exceptionalism*, 107 Cornell L. Rev. 627 at 639; Zettler et al., *Mifepristone, Preemption, and Public Health Federalism*, 9 J. L. & Biosciences at 7.

system, FDA has reevaluated and revised the mifepristone REMS, including the ETASU, on multiple occasions. In 2016, FDA amended the REMS by allowing certain non-physician healthcare providers to prescribe and dispense mifepristone and by removing the requirement for prescribers to report non-fatal adverse events to the manufacturer. *See* FDA, *Risk Evaluation and Mitigation Strategy (REMS) for NDA 20687*, at 2-4 (Mar. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf. The revised patient agreement no longer required patients to take either mifepristone or misoprostol in their providers' office. *Cf.* FDA, *Risk Evaluation and Mitigation Strategy (REMS) for NDA 20687*, at 8 (Mar. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf.

Upon its approval in 2019, GenBioPro, Inc.'s generic version of mifepristone became subject to the mifepristone REMS. FDA established a single, shared system REMS for both branded and generic mifepristone. *See* FDA, *Risk Evaluation and Mitigation Strategy (REMS) Single Shared System for Mifepristone 200 MG* (Apr. 2019), https://www.fda.gov/media/164650/download.[13]

[13] ANDA applicants referencing a drug with a REMS with ETASU generally must use a "single, shared system" with an NDA holder. 21 U.S.C. § 355-1(i)(1)(C). FDA considers single shared system REMS to benefit drug applicants, health care providers, and patients alike. Such a system "provid[es] opportunities for sharing the cost of developing and implementing the [REMS] program," and it allows for a "single set of REMS materials and information about the program." FDA, *Draft Guidance for Industry, Development of a Shared System REMS*, at 3-4 (June 2018), https://www.fda.gov/media/113869/download.

In December 2021, FDA concluded that "the [mifepristone] REMS *must* be modified to remove the in-person dispensing requirement" so as to "render the REMS less burdensome to healthcare providers and patients." Response Letter from P. Cavazzoni, Dir., FDA, to D. Harrison, Exec. Dir., Am. Ass'n of Pro-Life Obstetricians & Gynecologists Denying Citizen Petition, at 35 (Dec. 16, 2021) ("Citizen Petition Response"). The January 2023 REMS permanently removed the in-person dispensing requirement and added a new certification process for retail pharmacies to dispense mifepristone to patients. *See* FDA, *Risk Evaluation and Mitigation Strategy (REMS) Single Shared System for Mifepristone 200 MG*, at 1 (Jan. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2023_01_03_REMS_Full.pdf.[14] Mifepristone still cannot be dispensed at non-certified pharmacies, and all other ETASU from the 2016 REMS remain in effect (e.g., prescriber certification and completion of Prescriber and Patient Agreement Forms).

Notably, in setting the national terms for accessing mifepristone, FDA expressly considered and rejected requests to re-impose certain restrictions included in prior versions of the mifepristone REMS. In the 2021 Citizen Petition Response, for example, FDA denied petitioners' request to reverse the 2016

[14] Certification requires, among other things, that a pharmacy agree to certain record keeping, reporting, and medication tracking efforts and designate a compliance representative to implement these measures. *See id.* at 3-4, 11-12.

changes to the mifepristone REMS. *See* 2021 Citizen Petition Response at 7-19. FDA also expressly considered and rejected claims that mifepristone could not be dispensed safely through telemedicine, determining that data submitted through the REMS program and the published literature demonstrate that the in-person dispensing requirement is no longer necessary to ensure that the benefits of the drug outweigh the risk. *See id.* at 22, 25-36. Nonetheless, FDA continues to tightly restrict the prescribing and dispensing of mifepristone by requiring healthcare provider and pharmacy certification.

Consistent with its statutory authorities, FDA has regulated mifepristone from development to approval, and through prescribing, dispensing, and use. This end-to-end regulation is exceptional and rare (of the thousands of prescription drugs FDA has approved, currently there are only 64 REMS with ETASU[15]), and can only be mandated by FDA through the REMS with ETASU powers Congress granted the Agency under FDAAA. Since mifepristone's initial approval, FDA has had to consider how to maintain national availability using the least restrictive means to assure patient safety. The statute does not permit states to undermine or interfere with the access determinations FDA has established under its section 505-

[15] *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 Feb. 11, 2024). Certain REMS are applicable to multiple applications. *See id.*

1(f) authorities by imposing additional restrictions and concomitant burdens on either patients or the healthcare delivery system.[16] West Virginia's law does exactly this. It creates extreme burdens in accessing mifepristone that are not justified based on its safety and efficacy, contradicting a comprehensive federal regulatory scheme mandated by Congress. Allowing states to impose additional restrictions on mifepristone access would defeat Congress's very purpose in creating REMS with ETASU: finding a delicate balance between drug safety and ensuring patient access to necessary drugs.

CONCLUSION

For the reasons discussed herein, the district court's preemption analysis is flawed. Its order should be reversed.

[16] Moreover, the district court's determination that HCPs could simply abide by the state restrictions in addition to the ETASU in the mifepristone REMS is legally unsound. Since the West Virginia law effectively bans prescribing of mifepristone in almost all circumstances, the only way HCPs could abide with both sets of restrictions is to stop prescribing, i.e., "stop selling," the drug in nearly every circumstance—a "solution" the district court correctly noted has been rejected by the Supreme Court. *See* JA271 (citing *Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472, 488 (2013)).

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Respectfully submitted,

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UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

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