Nos. 24-1576(L), 24-1600, 24-1617

IN THE UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

AMY BRYANT, M.D.,
PLAINTIFF-APPELLEE,

V.

TIMOTHY K. MOORE, *et al.*,
INTERVENORS/DEFENDANTS-APPELLANTS,

AND

JOSHUA H. STEIN, in his official capacity as Attorney General for the State of North Carolina, *et al.*,
DEFENDANTS-APPELLEES.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA

BRIEF FOR THE DISTRICT OF COLUMBIA, MASSACHUSETTS, CALIFORNIA, COLORADO, CONNECTICUT, DELAWARE, ILLINOIS, MAINE, MARYLAND, MICHIGAN, MINNESOTA, NEW YORK, NEW JERSEY, OREGON, PENNSYLVANIA, RHODE ISLAND, VERMONT, AND WASHINGTON AS AMICI CURIAE IN SUPPORT OF APPELLEES

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes and Regulations

Other Authorities

INTRODUCTION AND INTEREST OF AMICUS CURIAE

The District of Columbia, Massachusetts, California, Colorado, Connecticut, Delaware, Illinois, Maine, Maryland, Michigan, Minnesota, New York, New Jersey, Oregon, Pennsylvania, Rhode Island, Vermont, and Washington ("Amici States") submit this brief in support of appellees and affirmance of the district court's judgment. Amici States oversee "the protection of the lives, limbs, health, comfort, and quiet of all persons" within their borders. *Medtronic Inc. v. Lohr*, 518 U.S. 470, 475 (1996) (quoting *Metro. Life Ins. Co. v. Massachusetts*, 471 U.S. 724, 756 (1985)). Our jurisdictions are home to hospitals, clinics, and other state-run facilities that provide health care to millions of patients. As a result, Amici States have decades of collective experience implementing evidence-based medical treatment consistent with and, at times, beyond those requirements imposed by the federal Food & Drug Administration ("FDA").

Mifepristone is an evidence-based treatment that is critical to reproductive health. Decades of clinical research have confirmed that it is safe and effective. Indeed, millions of Americans have relied on mifepristone to end their early pregnancies and to treat miscarriages. Amici States know that when one jurisdiction restricts access to reproductive health care, neighboring states suffer the downstream effects of patients traveling out-of-state to seek treatment. Amici States therefore

have a strong interest in ensuring the availability of high-quality, data-driven medical care—including access to mifepristone.

This case concerns whether a state can revive purported safety-based restrictions on mifepristone that the FDA, acting under express statutory authority, has both considered and rejected as unnecessary to protect safety. The answer to that narrow question is "no." To be sure, preserving the proper balance between state and federal authority over regulated drugs like mifepristone can be a difficult task. But in this case, the district court struck that balance in a careful opinion that preserves Congress's objective of protecting patient access to essential reproductive health care without trammeling states' rights. The district court's judgment should be affirmed.

SUMMARY OF ARGUMENT

1. Mifepristone is a critical component of basic reproductive health care. Since its FDA approval more than two decades ago, millions of Americans have relied on mifepristone to end their early pregnancies. Today, mifepristone is the most common method for terminating first-trimester pregnancies in the United States. Hundreds of clinical studies have demonstrated that mifepristone is safe, effective, and essential, particularly for patients who live in medically underserved areas. By imposing restrictions on mifepristone that limit access without improving patient safety, North Carolina's regulations will only harm people's health. Barriers

to mifepristone access increase patient wait and travel times, push abortions later into pregnancy, and drive up costs and medical risks.

Mifepristone restrictions also push patients to seek out-of-state providers, clinics, pharmacies, and telemedicine services. Jurisdictions have already had to expand their capacity to provide post-*Dobbs* reproductive care to patients coming from states with limited abortion access. Allowing states to impose needless mifepristone restrictions will further strain neighboring jurisdictions' medical capacities, worsening health outcomes for everyone seeking essential health care.

2. North Carolina's mifepristone regulations that replicate restrictions expressly considered and rejected by the FDA as hindering access and unnecessary to protect patient safety are preempted. Under straightforward obstacle preemption principles, a state may not enact laws that interfere with Congress's purposes and objectives. Congress has given the FDA the regulatory authority to establish additional conditions under which certain drugs can be used, with an explicit objective of expanding patient access within bounds necessary to ensure drug safety. Under this congressional mandate, the FDA originally enacted restrictions that limited mifepristone providers to only physicians, and required in-person dispensation, in-person follow-up appointments, and reporting of any adverse events. After determining from decades of evidence that those restrictions limited access while neither improving patient safety nor adequately balancing efficacy with

minimizing burdens on the health care system, the FDA rescinded these restrictions on access. North Carolina's revival of the same restrictions on purported safety grounds is therefore preempted.

3. The major questions doctrine does not apply in this case because the relevant statute is clear, and FDA's regulation does not implicate any major question. In 21 U.S.C. § 355-1, Congress provided express authorization for the FDA to create a Risk Evaluation and Mitigation Strategy ("REMS") for specific drugs. And the FDA acted pursuant to this grant of authority when it promulgated, and later modified, the REMS program for mifepristone. In doing so, the FDA acted narrowly in accordance with decades of prior practice. It did not undertake the kind of "transformative expansion" of regulatory authority needed to trigger the major questions doctrine. That doctrine cannot be invoked to override plain statutory text.

ARGUMENT

I. Mifepristone Is A Safe And Integral Component Of Reproductive Health Care.

A. Mifepristone has been safely and widely used for decades.

In Amici States' experience, mifepristone is safe, effective, and integral to reproductive health care. Since its approval by the FDA in 2000, more than five million people in the United States have relied on mifepristone to end their early

pregnancies.[1] Today, mifepristone accounts for the majority of abortions performed in the country.[2] The drug is also used to medically treat early pregnancy loss and to help patients manage their miscarriages.[3]

Over the last quarter century, mifepristone has become one of the most studied drugs prescribed in the country.[4] Mifepristone has been assessed in more than 630 published clinical trials, of which two-thirds were randomized control studies, considered to be "the gold standard in research design."[5] Decades of evidence-based research from around the world has repeatedly demonstrated that medication abortion is safe and effective, with mifepristone having a success rate of over 96% and complications arising in less than "a fraction of a percent of patients."[6] The World Health Organization ("WHO") even includes the mifepristone/misoprostol

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1 U.S. Food & Drug Admin., *Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2022*, https://tinyurl.com/yc5amd78.

2 Katherine Kortsmit et al., *Abortion Surveillance — United States, 2021*, 72 Morbidity & Mortality Wkly Rep. Surveillance Summaries, no. 9, Nov. 24, 2023, https://tinyurl.com/ju9bsfy3.

3 *See* Courtney A. Schreiber et al., *Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss*, 378 New Eng. J. Med. 2161 (2018), https://tinyurl.com/4kbvuc4x.

4 David S. Cohen et al., *Abortion Pills*, 76 Stan. L. Rev. 317, 326 (2024).

5 Brief for American College of Obstetricians & Gynecologists et al. as Amici Curiae in Support of Petitioners at 13-14, *FDA v. All. for Hippocratic Med.*, 602 U.S. 367 (2024).

6 Nat'l Acads. of Scis., Eng'g & Med. ("NASEM"), *The Safety and Quality of Abortion Care in the United States* 55 (2018), https://tinyurl.com/4pw4wbpz.

regimen on its Model List of Essential Medicines—those "that satisfy the priority health care needs of a population" based on "evidence of efficacy and safety," and should therefore "be available in functioning health systems at all times."[7]

A comparative review of FDA data by the University of California, San Francisco determined that other common medications carry risks that are many times greater than the risks associated with mifepristone. Whereas the reported mortality rate of mifepristone when used for medical termination of pregnancy is 0.65 deaths per 100,000—even accounting for deaths unrelated to the medication itself[8]—the fatality rate of penicillin is 2 deaths per 100,000, or three times higher.[9] Phosphodiesterase type-5 inhibitors, which are used for erectile dysfunction and include Viagra, have a fatality rate of 4 deaths per 100,000 users, or six times the

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[7] World Health Org., *The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines, 24-28 April 2023*, at 1, https://tinyurl.com/bddc2pcr (hereinafter "24th WHO Expert Committee Report"); *see* World Health Org., *Web Annex A: WHO Model List of Essential Medicines—23rd List (2023)*, at 53, *in* 24th WHO Expert Committee Report, https://tinyurl.com/3rr4jppe.

[8] Because it is mandatory to report the death of any person who has used mifepristone, these reports capture concurrent causes of death such as homicide and suicide. Bixby Ctr. for Glob. Reprod. Health, Univ. of Cal., S.F., *Analysis of Medication Abortion Risk and the FDA report "Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2018,"* at 1 (Apr. 2019), https://tinyurl.com/3rekrsf7. If only the cases that appear to be related to the use of mifepristone for medical termination of pregnancy are included, the mortality rate is 0.35 deaths per 100,000 medication abortions. *Id.*

[9] *Id.* at 2.

rate for mifepristone.[10] And medication abortion is far safer than childbirth, which carries a mortality rate that is fourteen times higher.[11]

In addition to its efficacy, mifepristone offers significant benefits for patients. For instance, medication abortion promotes patient accessibility, flexibility, and privacy. Medication abortion also allows noninvasive access to abortion as early as possible, when it is the safest and least expensive for patients. In 2021, two-thirds of all abortions performed at nine weeks' gestation or earlier were done using medication abortion.[12] The ease of medication abortion also facilitates access for patients—often living in rural, low-income, or other medically underserved areas—who have difficulty receiving reproductive health care.[13] And medication abortion can be safely administered in a variety of settings, such as at a hospital, in a private physician's office, or at home under appropriate medical supervision.[14] This flexibility allows for greater privacy and security for patients and their providers.

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10 *Id.*

11 *Id.*

12 Kortsmit et al., *supra* note 2.

13 *See* Liza Fuentes & Jenna Jerman, *Distance Traveled to Obtain Clinical Abortion Care in the United States and Reasons for Clinic Choice*, 28 J. Women's Health 1623, 1627, 1630 (2019) (finding that patients in rural areas are eight times more likely than patients in non-rural areas to travel more than 100 miles to access reproductive care).

14 NASEM, *supra* note 6, at 58.

Despite mifepristone's proven safety and utility, the FDA has rigorously regulated and restricted access to mifepristone under REMS. 21 U.S.C. § 355-1. Of the more than 20,000 prescription drugs FDA has approved for marketing in the United States, it has required a REMS for only 320 of them.[15] By contrast, drugs with greater risk profiles, such as penicillin and Viagra, are not subject to REMS restrictions. Mifepristone's track record is so conclusive that leading medical experts, including the American College of Obstetricians and Gynecologists, have advocated for the removal of mifepristone REMS altogether because the restrictions create barriers to care without meaningfully improving safety.[16]

B. North Carolina's implementation of mifepristone restrictions rejected by the FDA creates unnecessary burdens to reproductive health care.

Limiting access to standard medical care will only harm patient health, not promote it. In 2023, North Carolina imposed a laundry list of restrictions on the use of medication abortion. N.C. Gen. Stat. § 90-21.80 *et seq.* These restrictions include requirements that the FDA had previously implemented, but later rescinded. *First*, North Carolina limits the universe of acceptable reproductive health care providers

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15 *FDA Risk Evaluation and Mitigation Strategy (REMS) Public Dashboard,* FDA (Oct. 8, 2024), https://tinyurl.com/muwht9bd.

16 *Improving Access to Mifepristone for Reproductive Health Indications*, Am. Coll. of Obstetricians & Gynecologists (June 2018, *reaffirmed* Mar. 2021), https://tinyurl.com/2fxyznjj.

to only physicians. *See id.* § 90-21.83B(a). *Second*, it compels an in-person examination prior to any "prescribing, administering, or dispensing" of mifepristone. *Id.* § 90-21.83B(a). *Third*, it further mandates an in-person follow-up appointment, with physicians having an affirmative obligation to "make all reasonable efforts to ensure that the woman returns for the scheduled appointment." *Id.* § 90-21.83B(b). *Fourth*, physicians must report any adverse events related to mifepristone to the FDA. *Id.* § 90-21.93(c).

The FDA rejected each of these requirements years ago after determining that they failed to improve patient safety while burdening the health care system. Today, the FDA allows health care providers, not just physicians, to prescribe mifepristone so long as providers are appropriately licensed.[17] Further, patients may acquire mifepristone from certified pharmacies.[18] And after decades of evidence collected from clinical studies, the FDA now requires reporting only fatalities—not *any*

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[17] U.S. Food & Drug Admin., *Risk Evaluation and Mitigation Strategy (REMS) for NDA 20687 Mifeprex (mifepristone) Tablets, 200 mg*, at 1-4 (Mar. 2016), https://tinyurl.com/bd93hcpv (hereinafter "2016 REMS").

[18] U.S. Food & Drug Admin., *Risk Evaluation and Mitigation Strategy (REMS) Single Shared System for Mifepristone 200 mg*, at 2-5 (Mar. 2023), https://tinyurl.com/5n88zk9b.

adverse events—because mifepristone's safety profile is so "well-characterized" and "essentially unchanged."[19]

In practice, North Carolina's mifepristone restrictions eliminate telemedicine options and pharmacy dispensing, strain physicians who are already over capacity, and produce a chilling effect on health care professionals.[20] These regulations also increase wait times and travel times for accessing medication abortion, push abortions later into pregnancy, and drive up patient costs and medical risks.[21] These effects will worsen health outcomes and compound existing racial and economic health disparities, especially for patients in medically underserved areas.[22]

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[19] Letter from Patrizia A. Cavazzoni, Dir., Ctr. for Drug Evaluation & Rsch., FDA, to Donna J. Harrison, Exec. Dir., Am. Assoc. of Pro-Life Obstetricians & Gynecologists, and Quentin L. Van Meter, President, Am. Coll. of Pediatricians 20 (Dec. 16, 2021), https://tinyurl.com/yhwv5epp.

[20] *See* Rachel Crumpler, *One year into new abortion limits, N.C. patients and providers struggle to shoulder the load restrictions bring*, N.C. Pub. Radio (July 2, 2024), https://tinyurl.com/4z6efuut.

[21] Rachel Crumpler, *Access to abortion fraught with more logistical challenges as patients confront increased restrictions*, N.C. Health News (Dec. 8, 2023), https://tinyurl.com/3brzxnsj.

[22] *See* Diana Greene Foster et al., *Socioeconomic Outcomes of Women Who Receive and Women Who Are Denied Wanted Abortions in the United States*, 112 Am. J. Pub. Health 1290, 1296 (2022) (concluding that abortion restrictions "may result in reductions in full-time employment, increased incidence of poverty, more women raising children alone, and greater reliance on public assistance," with a net result of "serious adverse economic consequences for women and children").

Curtailing access to mifepristone—the safest and most common method used for first-trimester abortions—would only exacerbate disruptions to reproductive care in the wake of *Dobbs*. In the two years since the Supreme Court overruled *Roe v. Wade*, at least twenty-one states have outright banned abortion or restricted access beyond the standard set by *Roe*.[23] Ten states have bans with no exceptions for pregnancies resulting from rape or incest.[24] Five states have no exceptions for the pregnant person's health.[25] States with restrictive abortion access are home to 32 million women of reproductive age—nearly half of all women in the United States between the ages of 15 and 49.[26] This has resulted in an outsized demand on the health care systems of states with less restrictive abortion access laws. Despite severe obstacles, the total number of abortions performed nationally has *increased*, even as abortion became nonexistent in many states.[27] In fact, more abortions were performed in the first quarter of 2024 than in any other time period since *Dobbs*,

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[23] Allison McCann & Amy Schoenfeld Walker, *Tracking Abortion Bans Across the Country*, N.Y. Times (updated Sept. 30, 2024), https://tinyurl.com/4uezm7vk.

[24] *See State Bans on Abortion Throughout Pregnancy*, Guttmacher Inst. (updated Oct. 7, 2024), https://tinyurl.com/4hs97kdx.

[25] *See id.*

[26] Nigel Madden et al., *Post*-Dobbs *Abortion Restrictions and the Families They Leave Behind*, 114 Am. J. Pub. Health 1043, 1044 (2024).

[27] Soc'y of Fam. Plan., *#WeCount Report April 2022 to March 2024*, at 2 (Aug. 7, 2024), https://tinyurl.com/5bcckhex.

with New York, California, Virginia, Kansas, and Pennsylvania experiencing the sharpest increases.[28]

This heightened volume has resulted in many Amici States experiencing strained medical resources—particularly as patients turn to jurisdictions where abortion remains legally protected.[29] Although providers have endeavored to meet rising demand, patients nevertheless encounter limited practitioner capacity and longer wait times.[30] Allowing North Carolina to impose medically unnecessary restrictions on mifepristone will drive even more patients to seek out-of-state medication abortion, including into some of Amici States.

These harms are not hypothetical. In the month after North Carolina implemented its abortion restrictions, the number of abortions provided in the state dropped by 31%.[31] Meanwhile, thousands of North Carolina residents sought care outside of the state.[32] Virginia, one of the most common destinations for North Carolina patients, has experienced a shortage of medical providers and delays to

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28 *Id.* at 2, 5.

29 Laura Kusisto, *Women Encounter Abortion Delays as Clinics Draw Patients From Out of State*, Wall St. J. (Feb. 12, 2023), https://tinyurl.com/bdffdhap.

30 *Id.*

31 Rachel Crumpler, *A clearer picture is emerging of the impact of North Carolina's new abortion restrictions,* N.C. Health News (Oct. 11, 2023), https://tinyurl.com/3fmzked6.

32 *Monthly Abortion Provision Study – North Carolina*, Guttmacher Inst., https://tinyurl.com/2v2zej2v.

patient care due to rising out-of-state demand.[33] These ripple effects will continue to spread to other jurisdictions and may jeopardize health care delivery for some of Amici States' own residents.

II. The District Court Properly Concluded That North Carolina's Restrictions On Access To Mifepristone Are Preempted.

Under the Supremacy Clause, U.S. Const. art. VI, cl. 2, states may not enact laws that "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). At the same time, States have significant police power to regulate health and safety within their borders, and routinely do so on matters spanning across the realms of public health, medicine, and medical licensure. *See Hillsborough County v. Automated Med. Labs, Inc.*, 471 U.S. 707, 719 (1985).

Conflict preemption, like all forms of preemption, is predominantly a question of legislative interpretation and congressional intent. To determine whether "an agency regulation with the force of law" preempts state laws, courts "rely[] on the substance of state and federal law." *Wyeth v. Levine*, 555 U.S. 555, 576 (2009). And where the state law creates an actual conflict with federal objectives—including "important means-related federal objectives" such as the necessity of certain types

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[33] Sam Cabral, *Abortion: Pressure grows on Virginia as new bans arise in the south*, BBC (May 18, 2023), https://tinyurl.com/y887nsrd.

of regulation—the state law is preempted. *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 881 (2000).

An example of such a circumstance is *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000). In *Geier*, the Department of Transportation ("DOT"), pursuant to its authority under the National Traffic and Motor Vehicle Safety Act of 1966, considered but expressly declined to adopt a rule requiring car manufacturers to install airbags in *all* of their vehicles. 529 U.S. at 878. The agency elected instead to allow manufacturers to choose among different "passive restraint mechanisms" such as airbags, automatic seatbelts, or other passive restraint technologies. *Id.* Consistent with decades of prior regulatory actions, DOT had determined that providing manufacturers with "a range of choices among different passive restraint devices," rather than requiring airbags, would best promote the statute's safety objectives. *Id.* at 875, 868. The agency determined that this would, consistent with congressional objectives, "lower costs, overcome technical safety problems, encourage technological development, and win widespread consumer acceptance." *Id.* at 875; *see id*. at 881 (identifying the federal purpose as a "policy judgment that safety would be best promoted if manufacturers installed alternative protection systems in their fleets rather than one particular system in every car"). As a result, a state tort lawsuit alleging that manufacturers had been negligent for failing to install airbags was preempted because it would *require* an all-airbag rule for all

vehicles in conflict with the agency's explicit decision to decline such a rule. *Id*. at 886, 879. Indeed, the tort lawsuit "would have presented an obstacle to the variety and mix of devices that the federal regulation sought." *Id*. at 881.

In contrast, *Wyeth v. Levine*, 555 U.S. 555 (2009), illustrates circumstances in which a state acting in the same field is not preempted by federal regulation. There, the Supreme Court addressed the preemptive effect of a different set of federal regulations promulgated by the FDA. A state tort lawsuit alleged that a drug manufacturer had been negligent because its drug label failed to adequately warn of certain health risks. *Wyeth*, 555 U.S. at 558. The Court declined to endorse the manufacturer's position that the lawsuit was preempted because it would have required safety warnings beyond those required by the FDA. The Court declined to find the requisite actual conflict, noting that for most drugs approved by the FDA, Congress made clear that *drug manufacturers,* rather than the agency, were at all times responsible for updating their prescription drug labels based on safety information that became available after the FDA's initial approval of the drug. *Id.* at 567-68. Furthermore, Congress had recognized the utility of state common-law tort lawsuits in uncovering unknown drug hazards and providing incentives for manufacturers to disclose safety risks voluntarily and promptly. *Id.* at 579. Therefore, the Court noted, Congress declined to enact an express preemption provision for prescription drugs, although it had enacted such a provision for medical

devices in the same statute. *Id.* at 567. In contrast to *Geier*, the Court found that there was no record of the FDA's weighing and balancing of factors in approving the drug label. In other words, the FDA had never "consider[ed] and reject[ed] a stronger warning" on the drug's label, because the manufacturers, not the FDA, bore primary responsibility for their drug labeling. *Id*. at 581 n.14. This absence of consideration by the FDA made the record in *Wyeth* "quite different" from the agency action considered in *Geier*. *Id.* at 580.

Here, Congress has expressly tasked the FDA with ensuring that Americans can access certain drugs—what plaintiff refers to as "REMS drugs"—and can do so safely. The Federal Food, Drug, and Cosmetic Act ("FDCA") directs the FDA to approve a drug that is shown to be safe and effective when used as directed in the drug's labeling. 21 U.S.C. § 355(d). But in 2007, in the Food and Drug Administration Amendments Act ("FDAAA"), Congress went further and tasked the FDA with setting specific conditions on the use of a subset of medications whose significant benefits can only be realized if certain precautions or limitations are observed. For these drugs, the FDA is tasked with establishing a REMS for the specific purpose of "ensur[ing] that the benefits of [a] drug outweigh the risks." 21 U.S.C. § 355-1(a)(1). Congress also gave the FDA authority to impose "elements to assure safe use" ("ETASUs") for drugs with "inherent toxicity or potential harmfulness." *Id.* § 355-1(f). Further, Congress mandated that when the agency

includes ETASUs, the restrictions must "not be unduly burdensome on patient access to the drug," and must, "to the extent practicable[,] minimize the burden on the health care delivery system." *Id.* § 355-1(f)(2)(C) to (D). Under the FDAAA, in other words, and for the specific set of drugs to which it applies, FDA is expressly required to analyze both the risks associated with a drug and the on patients in order to determine the least restrictive set of requirements that will ensure safety while maximizing access.

For over two decades, the FDA has tightly monitored and restricted mifepristone's prescription, distribution, and dispensation pursuant to its authority under the FDCA and FDAAA. In September 2000, the FDA first approved the use of mifepristone, in combination with misoprostol, for the medical termination of intrauterine pregnancy through 49 days' gestation.[34] This initial approval followed an extensive three-cycle review process that spanned more than 54 months.[35] In comparison, the average approval period for new drug applications during this time was around 18 months.[36]

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[34] Letter from Ctr. for Drug Evaluation & Rsch. to Sandra P. Arnold, Vice President, Population Council 1 (Sept. 28, 2000), https://tinyurl.com/3b8vbce9 (hereinafter "2000 Approval Letter").

[35] *See* U.S. Gov't Accountability Off., Food and Drug Administration Approval and Oversight of the Drug Mifeprex 5, 27 (Aug. 2008), https://tinyurl.com/yhwz2a8w (hereinafter "2008 GAO Report").

[36] *Id.* at 27.

With the 2000 approval, the FDA implemented restrictions on mifepristone under its Subpart H regulations. 21 C.F.R. § 314.500. Mifepristone could be administered only in a clinic, medical office, or hospital, and by or under the supervision of a qualified physician.[37] All qualified mifepristone providers were further required to sign a prescriber's agreement that they met certain requirements and to agree to a series of procedural restrictions. These included conducting a follow-up appointment with the patient after two weeks and notifying the manufacturer of any failed pregnancy termination, as well as any "hospitalization, transfusion, or other serious event" associated with treatment.[38]

These restrictions largely remained in place following Congress's passage of the FDAAA. When the FDA first approved the mifepristone REMS in 2011, it largely adopted the same restrictions from the drug's approval in 2000.[39] Over the intervening decade, and under its express statutory obligation to ensure that its regulations are not "unduly burdensome on patient access," 21 U.S.C. § 355-1(b)(5), (f)(1)(A), the FDA has subjected the mifepristone REMS to numerous rounds of

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37 *See* 2000 Approval Letter, *supra* note 34, at 2.

38 2008 GAO Report, *supra* note 35, at 48-49.

39 *See* 2016 REMS, *supra* note 17, at 1-2, 5. The manufacturer of Mifeprex—the brand name of mifepristone—submitted the first draft of a proposed REMS for Mifeprex on September 16, 2008. The FDA's review of the proposed REMS was extensive—lasting nearly three years and through four rounds of review. *See* U.S. Food & Drug Admin., *Supplement Approval for NDA 020687/S-014* at 1 (June 8, 2011), https://tinyurl.com/3p6tnm62.

reevaluation and has ultimately withdrawn several restrictions—the very same restrictions that North Carolina now seeks to revive.

First, the FDA no longer requires that mifepristone be prescribed by physicians only and administered in-person in a physician's presence. In 2016, the FDA began allowing a broader set of health care providers, such as nurse practitioners and physician assistants, to be certified to prescribe the drug.[40] In rescinding the physician-only restriction, FDA experts conducted an extensive analysis of peer-reviewed literature and found no difference in mifepristone's safety and efficacy when prescribed by physicians versus other qualified health care providers.[41] In 2021, the FDA further removed the in-person dispensing requirement. This effectively allowed mifepristone to be prescribed remotely by a certified prescriber and sent to the patient via mail.[42] Based on the available data, the FDA determined that these REMS modifications were necessary "to reduce

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[40] *See* 2016 REMS, *supra* note 17, at 2-4. In addition, the FDA extended the gestational age for which mifepristone was approved for use from 49 days to 70 days, modified the dosing regimen for mifepristone and misoprostol, and removed the requirement for additional office visits. *See* Ctr. for Drug Evaluation & Rsch., *NDA 20-687: Labeling—Highlights of Prescribing Information for Mifeprex (Mifepristone) Tablets* 2-4 (Mar. 29, 2016), https://tinyurl.com/y9wwjmuw.

[41] *See, e.g.*, Ctr. for Drug Evaluation & Rsch., *NDA 20-687: Summary Review for Regulatory Action* 16-17 (Mar. 29, 2016), https://tinyurl.com/23fsdhrv (hereinafter "2016 Summary Review").

[42] *See Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation*, FDA (updated Sept. 1, 2023), https://tinyurl.com/5dzujwkv.

burden on the health care delivery system and to ensure the benefits of the product outweigh the risks."[43]

Second, the FDA removed its original requirement that prescribers schedule follow-up office visits for patients after administering mifepristone. In 2016, at the same time that it allowed a broader set of certified prescribers to dispense the drug, FDA experts also determined, based on review of available data, that "no literature" indicated that follow-ups improved patient safety.[44]

Third, the FDA also narrowed the rule requiring providers to report "any hospitalization, transfusion, or other serious event."[45] Now, the FDA requires providers and mifepristone manufacturers to report only fatalities to the agency.[46] Once again, the FDA experts unanimously agreed from their comprehensive review of existing literature that the rates of serious adverse events were "well below 1%."[47]

Importantly, in 2021, the FDA expressly considered and rejected requests to reimpose all three of these restrictions from its original REMS. The FDA conducted a comprehensive review of data and found no support for reviving the restrictions.[48]

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43 *Id*.

44 2016 Summary Review, *supra* note 41, at 12.

45 2008 GAO Report, *supra* note 35, at 48-49.

46 *See* 2016 REMS, *supra note* 17, at 5.

47 2016 Summary Review, *supra* note 41, at 11.

48 *See* Letter from Patrizia A. Cavazzoni, *supra* note 19, at 2-3, 9-15, 20-21.

In doing so, the FDA appropriately exercised its statutory authority to reevaluate mifepristone's ETASUs to ensure that restrictions are not "unduly burdensome on patient access to the drug" and "minimize the burden on the health care delivery system," 21 U.S.C. § 355-1(f).

These clear congressional objectives and the extensive record make this case a straightforward one under traditional obstacle preemption principles. Contrary to the argument of appellants' amici, *see* Iowa Amicus Br. 12, the district court's logic does not mean that REMS requirements will always set the ceiling for regulation of a given drug. *Geier* does not say that once an agency adopts *some* safety requirements, all others are off the table. Rather, as *Geier* explains, the analysis turns on whether a state law "actually conflicts" with federal objectives. *Geier*, 529 U.S. at 874. Nobody can contend that this is a scenario in which "the record shows that the FDA has paid very little attention to the issues" addressed by North Carolina's regulations. *Wyeth*, 555 U.S. at 581 n.14. Instead, each of the restrictions that the district court held preempted was one that "the FDA did [] consider and reject," and one that conflicts with the statutory objectives of maximum safe access. *Id.*

As a result, there is little risk that affirming the district court's holding would mean that "any [FDA] drug approval would render additional State safety standards likely unavailable." Iowa Amicus Br. 12. States, in accordance with their historic

police powers, may still enact comprehensive health and safety regulations. For example, with respect to opioids, the FDA itself has expressed that opioid REMS are "one strategy among multiple national and state efforts to reduce the risk of abuse, misuse, addiction, overdose, and deaths due to prescription opioid analgesics."[49] In other circumstances, the statute, the agency's regulatory practice, and the terms of the regulation itself will reflect that state laws create no "actual conflict" with federal objectives and are not preempted. Here, however the FDA determined that these particular restrictions to access would create an obstacle to Congress's goal of expanding access to critical drugs within bounds necessary to preserve public safety. Against the backdrop of the specific FDA regulatory history at issue here, North Carolina may not replicate the rescinded REMS restrictions.

III. The District Court Correctly Determined That The Major Questions Doctrine Is Not Implicated In This Case.

Contrary to the arguments of appellants' amici, *see* Iowa Amicus Br. 17-20, the major questions doctrine does not apply here because the relevant statute is clear, and FDA's regulation does not implicate any major question. In 21 U.S.C. § 355-1, Congress provided express authorization for the FDA to create a REMS plan for certain drugs. Pursuant to Section 355-1, the FDA promulgated, and later modified, the mifepristone REMS. Adjusting these drug restrictions in accordance with

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[49] *Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)*, FDA (Nov. 14, 2023), https://tinyurl.com/3nt7pf4c.

scientific literature was nothing more than routine agency action—far from the kind of "transformative expansion" of regulatory authority needed to trigger the major questions doctrine. *West Virginia v. EPA*, 597 U.S. 697, 724 (2022).

A. Section 355-1 is clear.

The Supreme Court has applied the major questions doctrine only in "extraordinary cases" involving "agencies asserting highly consequential power beyond what Congress could reasonably be understood to have granted." *Id.* The doctrine has been reserved for circumstances in which agencies claim vast grants of authority based upon "'modest words,' 'vague terms,' or 'subtle device[s],'" and where the "history and the breadth" of that asserted power provide "reason to hesitate before concluding that Congress" meant to confer such authority. *Id.* at 721, 723-24 (internal citations omitted).

But here, it is undisputed that mifepristone falls within the category of FDA-regulated REMS drugs. *See* FDAAA § 909(b)(1), 121 Stat. at 950-51. And Congress provided express authorization for the FDA to dictate by whom, where, when, and how a REMS drug can be prescribed, dispensed, and administered. *See* 21 U.S.C. §§ 355-1(f)(3)(A) to (C). To give just a sample, Section 355-1 empowers the FDA to require that "health care providers who prescribe [a] drug have particular training or experience." *Id.* § 355-1(f)(3)(A). Further, the FDA can mandate that "pharmacies, practitioners, or health care settings that dispense the drug are specially

certified." *Id.* § 355-1(f)(3)(B). The FDA may limit drug dispensation to "certain health care settings, such as hospitals," or it may choose not to. *Id.* § 355-1(f)(3)(C). Thus, the FDA has statutory authorization to place restrictions on access to mifepristone—just as it can decide that those restrictions are no longer necessary for safe use.

In addition, Section 355-1 mandates that the FDA balance drug safety with patient access when setting appropriate ETASUs. Congress's intent is made plain throughout Section 355-1's text and headings. The statute's operative text demands that ETASUs "not be unduly burdensome on patient access to the drug, considering in particular . . . patients who have difficulty accessing health care." *Id.* § 355-1(f)(2)(C). The accompanying headings underscore the point: The FDA must "[p]rovid[e] safe access for patients to drugs with known serious risks that would otherwise be unavailable," *id.* § 355-1(f), and "[a]llow[] safe access to drugs with known serious risks," *id.* § 355-1(f)(1), while "[a]ssuring access and minimizing burden[s]," *id*. § 355-1(f)(2).

Through Section 355-1, Congress expressly made the FDA responsible for a comprehensive regulatory scheme that ensured both safety and access to mifepristone. Contrary to amici's contentions, Iowa Amicus Br. 19-20, this case is not like *Gonzales v. Oregon*, 546 U.S. 243 (2006). There, the Supreme Court held that the Attorney General was not delegated sole interpretive authority over the

meaning of an ambiguous provision like "legitimate medical purpose." *Id.* at 258, 265. Here, by contrast, Section 355-1 contains neither "vague terms" nor "subtle devices." *West Virginia*, 597 U.S. at 723. Instead, the statute is clear and direct. It means what it says. The FDA has the authority to promulgate and modify REMS for mifepristone, and it did just that.

B. The FDA acted narrowly pursuant to an express grant of authority from Congress when it promulgated and rescinded mifepristone regulations.

There is no question that abortion, as a general matter, is an issue of "vast 'economic and political significance.'" *Utility Air Reg. Grp. v. EPA*, 573 U.S. 302, 324 (2014) (internal citations omitted). But the major questions doctrine has never provided courts with the license to override plain statutory text simply because an agency's action may be economically or politically salient. Contrary to amici's assertions, the issue in this case is not whether the FDA should act as the "sole entity" deciding the "profound moral question" posed by abortion. Iowa Amicus Br. 18. Instead, the issue here is whether Congress gave the FDA license to create drug-specific regulations that balance safety with patient access. It did. Accordingly, the FDA acted narrowly within its delegated authority.

This case lacks the key features found in the limited instances where the Supreme Court has applied the major questions doctrine to hold that an agency overstepped its authority. *First*, the FDA's regulation of a discrete drug through a

REMS regulation generally will not be "transformative" or "sweeping" in a sense that would trigger the major questions doctrine. *West Virginia*, 597 U.S. at 721, 724. The FDA's actions here do not reorganize an entire sector of the economy, as in *West Virginia*, nor do they extend beyond the agency's traditional "reach," as was the case in *Alabama Association of Realtors*. *Second*, the FDA is not claiming an "unheralded power" buried within "a long-extant statute." *Utility Air Reg. Grp.*, 573 U.S. at 324; *accord FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000). Rather, the FDA's regulation of mifepristone has been ongoing for decades—as authorized by Congress, and as specifically ratified by Congress in 2007 through the FDAAA. *Third*, this is not a circumstance in which the FDA is operating in an area where it has "no expertise." *King v. Burwell*, 576 U.S. 473, 486 (2015). Unlike in *King v. Burwell*, where the Court held that the IRS had no place "crafting health insurance policy," determining appropriate drug regulations is the precise domain of the FDA. *Id.* Here, the agency was acting exactly as Congress intended and within the scope of its core expertise.

Finally, to the extent that appellants' amici argue that FDCA *preemption* in the REMS context is a major question, that is simply not true. The major questions doctrine is grounded in "separation of powers principles" governing relations between branches of the federal government. *West Virginia*, 597 U.S. at 700. By contrast, conflict preemption, by definition, involves the relationship between state

and federal laws. Nor is there any reason to think that *this* conflict preemption case raises a major question. Whether the FDA is regulating a pregnancy termination drug or an arthritis drug—both of which carry REMS—preemption principles must remain consistent.[50] Regulation of arthritis drugs and other quotidian treatments cannot possibly raise a major question, and preemption jurisprudence cannot switch on and off depending solely on the nature of the regulated drug.

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[50] *See Approved Risk Evaluation and Mitigation Strategies (REMS)*, FDA, https://tinyurl.com/2dswpm99 (listing all REMS drugs).

CONCLUSION

This Court should affirm the trial court's judgment.

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I hereby certify that on October 17, 2024, I electronically filed the foregoing amicus brief with the Clerk of the Court for the U.S. Court of Appeals for the Fourth Circuit using the CM/ECF system. All participants are registered CM/ECF users and will be served by the appellate CM/ECF system.

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