No. 24-1576(L)

In the United States Court of Appeals
for the Fourth Circuit

AMY BRYANT, M.D.,
Plaintiff-Appellee, Cross-Appellant

v.

TIMOTHY K. MOORE; PHILIP E. BERGER,
Intervenor-Defendants-Appellants, Cross-Appellees

and

JOSHUA H. STEIN, in his official capacity as Attorney General for the State of North Carolina,
Defendant-Appellee, Cross-Appellant

and

JEFF NEIMAN, in his official capacity as District Attorney for North Carolina 18th Prosecutorial District, et al.,
Defendants-Appellees.

On Appeal from the United States District Court
for the Middle District of North Carolina

REPLY BRIEF OF DEFENDANT ATTORNEY GENERAL JOSHUA H. STEIN

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INTRODUCTION

Legislative Intervenors do not dispute that, in a limited set of circumstances, federal law may preempt state laws that stand as obstacles to the purposes and objectives of Congress. To be sure, parties advancing arguments of this kind must carry a heavy burden. Dr. Bryant has done so here.

Under 21 U.S.C. § 355-1, Congress directed the Food and Drug Administration to ensure safe access to drugs with serious risks. In keeping with this goal, Congress empowered the FDA to create a set of risk-mitigation measures for such drugs that balance drug safety, patient access, and burdens on the healthcare delivery system. 21 U.S.C. § 355-1(f). In their briefing, however, Legislative Intervenors largely overlook this express congressional direction and instead proceed as though Congress were single-mindedly focused on drug safety.

It was not. Following Congress's express instruction to balance safety with access and burden, the FDA has developed detailed regulations for the prescription, dispensation, and administration of a select subcategory of drugs, one of which is mifepristone. On multiple

occasions since mifepristone's initial approval in 2000, moreover, the FDA has revised, reevaluated, and rescinded certain of its restrictions to achieve the carefully calibrated scheme in place today. North Carolina law, however, reimposes some of the same restrictions that the FDA adopted and then subsequently withdrew.

The Supreme Court has, time and again, affirmed that, in a narrow category of cases, States may not impose restrictions that a federal agency has "considered and rejected." *See* AG Opening/Response Br. 25-31. At the same time, the Court has made clear that, in applying these preemption principles, courts must respect state sovereignty on matters of health and safety. *Hillsborough Cnty. v. Automated Med. Labs. Inc.*, 471 U.S. 707, 718 (1985). The Attorney General's position adheres to both principles. As he has explained here and in an amicus brief in a related case pending before this Court: When States enact restrictions on certain REMS drugs that the FDA, under express statutory authority, has adopted and rescinded, those state laws necessarily have been considered and rejected by the FDA and are preempted. *See GenBioPro, Inc. v. Raynes*, No. 23-2194, Brief of Amicus Curiae the State of North Carolina in Support of Plaintiff-

Appellant (4th Cir. Feb. 14, 2024). Recognizing that the challenged state laws here interfere with the FDA's expert judgment in this way appropriately respects both the Supreme Court's obstacle-preemption precedent and state sovereignty on matters of health and safety.

Unable to find support for their arguments in the text of federal law or Supreme Court precedent, Legislative Intervenors stress the consequences of a ruling for Dr. Bryant. Specifically, they contend that if the challenged state laws regulating mifepristone are preempted, then so too are many other state laws regulating REMS drugs, including state laws seeking to curb opioid addiction and abuse. But this argument overlooks the important differences in the REMS governing opioids and mifepristone. As a coalition of 17 States and the District of Columbia explains, nothing in the obstacle-preemption arguments here calls into question the States' ordinarily broad police powers to protect health and safety, including with respect to other REMS drugs that do not share mifepristone's unique regulatory history. Amicus Br. of the District of Columbia & Massachusetts et al. 21-22.

The Attorney General respectfully requests that this Court affirm in part and reverse in part the decision below.

ARGUMENT

I. Longstanding Preemption Principles Require Finding That the Challenged State Laws Are Preempted

A. Supreme Court precedent controls the preemption analysis here.

Contrary to Legislative Intervenors' assertion, the Attorney General's test for obstacle preemption is not a "made-for-this-case-only view." Response/Reply Br. 7. Rather, it derives directly from Supreme Court precedent.

Specifically, the test that applies here comes from two Supreme Court cases: *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000), and *Wyeth v. Levine*, 555 U.S. 555 (2009). In *Geier*, the Court found preemption when a federal agency, seeking to balance competing considerations at Congress's direction, "rejected" the same safety requirements that state law sought to impose. 529 U.S. at 879. By contrast, in *Wyeth*, the Court found no preemption when, unlike in *Geier*, a federal agency had *not* "consider[ed] and reject[ed]" the state-law rule at issue. 555 U.S. at 581 n.14.

Legislative Intervenors misread both cases. In their view, *Geier*, read in light of *Williamson v. Mazda Motor of America, Inc.*, 562 U.S.

323 (2011), is "essentially limited . . . to its facts" and does not support preemption here—or seemingly in any other case. Response/Reply Br. 11-14. This argument lacks merit.

In *Geier*, the Supreme Court held that a state-tort suit against a car manufacturer for failing to install driver-side airbags was preempted by a Department of Transportation regulation that had declined to impose an airbag requirement on manufacturers. 529 U.S. at 881-82. The Court rooted this conclusion in the DOT's deliberations over whether to impose an all-airbag requirement. The agency, the Court explained, had sought to strike a balance among competing considerations: the public safety, the likelihood that the public would accept an airbag requirement, the prospect of technological advances, and the costs that such a rule could impose on car manufacturers and consumers. *Id.* at 877-79. This careful balancing led the DOT to consider and reject a rule that would have required all cars to have driver-side airbags and instead adopt a rule allowing manufacturers to install a varied mix of passive-restraint systems. *Id.* at 879. Given the DOT's decision to achieve this carefully calibrated balance, the Court

held that allowing state-tort suits that would require the installation of airbags would frustrate that objective. *Id.* at 881-82.

By contrast, in *Williamson*, the Supreme Court held that a different DOT regulation did *not* preempt a state-tort suit against a car manufacturer for failing to install lap-and-shoulder seatbelts, rather than lap seatbelts. 562 U.S. at 326. Unlike the DOT regulation in *Geier*, the DOT regulation in *Williamson* did not reflect the agency's efforts to carefully balance competing goals. *Id.* at 333-34. Although the DOT had declined to require car manufacturers to install lap-and-shoulder seatbelts, the Court explained that the agency had reached this conclusion only out of cost-effectiveness concerns. *Id.* at 335. But "[w]hile an agency *could* base a decision to pre-empt on its cost-effectiveness judgment," the Court was "satisfied that the rulemaking record at issue [in *Williamson*] disclose[d] no such pre-emptive intent." *Id.* (emphasis added).

Legislative Intervenors are wrong that *Williamson* renders *Geier* a one-off. Rather, in *Williamson*, Justice Breyer—the author of both opinions—specifically followed *Geier*'s framework of examining an agency regulation's "history" and "objectives." *Id.* at 330. The Court in

Williamson merely concluded that the objectives behind and the history of the particular federal regulation at issue did not evince an intent to preempt state law.

This case is like *Geier*, not *Williamson*. In *Williamson*, the inference of Congress's intent to preempt was weak: the DOT regulation there merely reflected the kind of "cost-effectiveness judgment" that underlies "many, perhaps most, federal safety regulations." *Id.* at 335. No such one-dimensional agency judgment is at issue here. The mifepristone REMS, just like the DOT regulation in *Geier*, reflects a deliberate balance among multiple competing considerations that the FDA has carefully calibrated over time.

If anything, the case for preemption here is even stronger than in *Geier*. Here, the FDA did not carefully balance competing objectives on just one discrete occasion when it originally approved mifepristone in 2000. It also—on multiple occasions—reviewed the original balance that it struck and repeatedly adjusted it to achieve an appropriate regulatory framework. This extensive regulatory history amply supports an inference of preemptive intent. *See Geier*, 529 U.S. at 881.

To be sure, Legislative Intervenors point out that in *Geier*, the Court gave "some weight" to the DOT's own understanding that its regulation had preemptive effect. 529 U.S. at 883; Response/Reply Br. 13. Here, by contrast, Legislative Intervenors claim that the FDA does not understand the mifepristone REMS to have preemptive effect. Response/Reply Br. 13-14. But Legislative Intervenors fail to establish the premise underlying this argument. The general FDA statements that they cite do not discuss the agency's view about preemption at all. Response/Reply Br. 13 & n.1 (citing JA 470).

Legislative Intervenors also cite the FDA's own stated view that the opioid REMS do not preempt state efforts to curb opioid abuse. Response/Reply Br. 13-14. Based on this agency position, Legislative Intervenors assume that the FDA's view is that *no drug's* REMS can ever have preemptive effect. But that inference is mistaken. The opioids REMS establish a different regulatory scheme than the mifepristone REMS, just as the regulations at issue in *Williamson* were different from those at issue in *Geier*. *See also infra* Part III. Moreover, the FDA's pronouncement that the opioid REMS do *not* preempt state law only fortifies the conclusion that if the FDA had meant for the

mifepristone REMS to also stand alongside other state regulatory schemes, it would have said so expressly.

As for *Wyeth*, Legislative Intervenors argue that the case stands for the proposition that, in cases involving FDA regulation, "federal law sets a federal floor" upon which States can add any additional regulations and conditions on top. Response/Reply Br. 16 (citing *Wyeth*, 555 U.S. at 565, 574, 579). That is simply not what *Wyeth* says. In fact, nowhere in the opinion does the Supreme Court characterize federal law involving drug safety as a "floor" or a "ceiling." Rather, *Wyeth* holds that the Food, Drug, and Cosmetic Act's *labeling* requirements do not prohibit state-tort law from imposing liability when drug manufacturers fail to update labels to reflect new safety information. 555 U.S. at 574. After all, under the FDCA, drug manufacturers, not the FDA, are ultimately responsible for updating label safety information. *Id.* at 568. But *Wyeth* predates the 2007 Amendments and involves labeling laws—laws that are entirely distinct from the statute directing the FDA to regulate REMS drugs. Therefore, *Wyeth* says nothing about the REMS statute, which imposes directly on the FDA an ongoing obligation to

carefully balance and reevaluate the tripartite goals of safety, access, and burden. 21 U.S.C. § 355-1(f)(5), (g).

As a result, Legislative Intervenors' attempt to characterize a drug's REMS as either a "floor" or "ceiling" is misguided. A drug's REMS do not represent minimum or maximum regulatory standards. Rather, they reflect the FDA's considered judgment about the unique balance between safety and accessibility that the FDA must strike for each REMS drug's distribution, prescription, and administration. For instance, the FDA may determine that particular disposal requirements are necessary for one drug, while different regulations about where a drug may be administered are essential for another. 21 U.S.C. § 355-1(e), (f). These decisions establish neither "floors" nor "ceilings." They instead result in a fine-tuned balancing of concerns about safety with concerns about access and burden, a federal objective that States cannot countermand. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347-48 (2001).

Legislative Intervenors also claim that *Wyeth*'s "considered-and-rejected" formulation is limited to "failure-to-warn" cases that concern impossibility preemption. Response/Reply Br. 14-15. But that

argument cannot be squared with *Wyeth*. Although *Wyeth* addressed both impossibility and obstacle preemption, the Court discussed whether the FDA had considered and rejected the labeling requirement at issue in the context of its obstacle-preemption analysis. 555 U.S. at 581 n.14 (rejecting argument that "this case resembles *Geier*" because the "FDA did not consider and reject a stronger warning"). Because this case does not involve impossibility preemption, *Wyeth*'s discussion of that different preemption theory is not relevant here.

In sum, the Supreme Court has repeatedly held that, in a narrow category of cases, States may not impose restrictions that a federal agency has considered and rejected as part of a comprehensive regulatory scheme. *See, e.g.*, *id.*; *Geier*, 529 U.S. at 878-79. Here, the challenged state laws impose rules that were once adopted and then later rescinded by the FDA. They are therefore preempted.

B. The challenged laws were adopted and rescinded by the FDA's mifepristone REMS and are therefore preempted.

Legislative Intervenors, under a variety of theories, insist that even if this Court were to apply ordinary obstacle-preemption principles

to the challenged state laws, the laws would still not be preempted. Response/Reply Br. 24-36. These arguments are unpersuasive.

To begin, Legislative Intervenors mischaracterize the Attorney General's position. The Attorney General is not arguing that the state laws here are preempted merely because the FDA did not include a given restriction in a REMS. Response/Reply Br. 26. As discussed above, under Supreme Court precedent, States may not impose restrictions that a federal agency has *affirmatively* considered and rejected as part of the agency's effort to implement a comprehensive regulatory scheme. *See supra* Part I.A. This occurs, at a minimum, when a federal agency has deliberately adopted and then rescinded the very regulations imposed by state law.

Legislative Intervenors next suggest that the challenged state laws are not preempted because the 2007 Amendments do not *specifically prohibit* what North Carolina law requires. *See, e.g.*, Response/Reply Br. 32 (asserting that because the FDA has never required in-person examination, a state law imposing that requirement does not present an obstacle to the 2007 Amendments); *id.* at 34 (arguing that, unless the FDA forbids States from passing informed-

consent provisions, there is no conflict).[1] To start, the carefully calibrated federal regulatory scheme to which the challenged laws pose an obstacle is the mifepristone REMS—not the 2007 Amendments. Moreover, this argument simply ignores the relevant legal test. To pose an obstacle to a carefully calibrated federal scheme, federal law need not prohibit what state law requires. That is impossibility preemption. Rather, state law is preempted when it poses an obstacle to a calibrated regulatory scheme. *See supra* Part I.A.

Finally, Legislative Intervenors argue that "minimally burdensome" state laws that promote safety can never present an obstacle to the mifepristone REMS. *See, e.g.*, Response/Reply Br. 34-35 (arguing that the waiting period requirements are "modest" and are not preempted because the "purpose of the FDAAA is not to get high-risk drugs to women as quickly as possible").[2] But that is not how preemption law works. Because a "[c]onflict in *technique* can be fully as

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[1] *See also* Response/Reply Br. 28 (similar, physician-only requirement); *id.* at 31 (similar, adverse-reporting requirement); *id.* at 33 (similar, blood-type requirement).

[2] *See also* Response/Reply Br. 28 (similar, in-person follow-up requirement); *id.* at 31 (similar, in-person examination requirement); *id.* at 33 (similar, blood-type requirement).

disruptive to the system Congress erected as a conflict in overt policy," a state law that advances the same objectives as federal law can still be preempted. *Amalgamated Ass'n of St., Elec. Ry. & Motor Coach Emps. of Am. v. Lockridge*, 403 U.S. 274, 287 (1971) (emphasis added). Here, the challenged laws impose conditions that the FDA adopted and then rescinded. Because the state laws interfere with the technique that the FDA chose in the mifepristone REMS to balance drug safety, access, and burden, they are preempted.

II. The 2007 Amendments Grant the FDA the Authority to Establish Fine-Tuned Regulations for REMS Drugs.

Legislative Intervenors also contend that the text of the 2007 Amendments does not support the conclusion that REMS requirements could have preemptive effect. They are right that the statutory text must anchor this Court's obstacle-preemption analysis. As the Supreme Court has explained, "evidence of preemptive purpose" must "be sought in the text and structure of the statute at issue." *Va. Uranium v. Warren*, 587 U.S. 761, 778 (2019) (lead opinion of Gorsuch, J.) (alterations omitted) (quoting *CSX Transp., Inc. v. Easterwood*, 507 U.S. 658, 664 (1993)); *id.* at 791-93 (opinion of Ginsburg, J.). But it is

Legislative Intervenors' own arguments that give short shrift to the text.

To begin, Legislative Intervenors seek to avoid the relevant text altogether. Pointing to the 1938 Food, Drug, and Cosmetic Act, Legislative Intervenors argue that Congress's "primary objective" was "to ensure the safety of food and drugs." Response/Reply Br. 5 (citing *Wyeth*, 555 U.S. at 574). That is true. AG Opening/Response Br. 53. But the relevant federal law here is the *2007 Amendments* to the FDCA. Specifically, the federal law that has preemptive effect is the provision of the 2007 Amendments that established the REMS program, 21 U.S.C. § 355-1. Legislative Intervenors concede that this is the textual "hook" for the preemption arguments in this case. Response/Reply Br. 8. Yet in their brief, Legislative Intervenors barely engage with section 355-1's text—they do not even quote the statutory language, instead citing the statute in passing on a few occasions. Response/Reply Br. 8, 18-19, 26.

When Legislative Intervenors do address the text, their arguments fall wide of the mark. In Congress's words, its purpose in passing the 2007 Amendments was to allow "safe access for patients to

drugs with known serious risks that would otherwise be unavailable." 21 U.S.C. § 355-1(f). To accomplish this purpose, Congress charged the FDA with imposing "elements as are necessary to assure safe use of the drug, because of its inherent toxicity or potential harmfulness." *Id.* § 355-1(f)(1). In doing so, Congress also required the FDA to, "considering such risk," ensure that these elements are not "unduly burdensome on patient access to the drug" and "minimize the burden on the health care delivery system." *Id.* § 355-1(f)(2)(C), (f)(2)(D).

Section 355-1 thus disproves Legislative Intervenors' argument that Congress had safety as its only concern in passing the 2007 Amendments, thus allowing States to enact any additional restriction presumably to promote safety. Response/Reply Br. 5. To the contrary, the 2007 Amendments expressly directed the FDA to balance drug safety against competing considerations, like the ability of patients to access REMS drugs and the burdens on the healthcare delivery system. Legislative Intervenors have no persuasive answer for these provisions of the 2007 Amendments. The text is incompatible with their repeated assertions that Congress sought to pursue a single-minded focus on drug safety. Response/Reply Br. 5, 7.

Legislative Intervenors respond that section 355-1(f) requires only the FDA—not States—to consider patient access to REMS drugs. Response/Reply Br. 8. But that is exactly the point. By charging the FDA with striking a balance between patient safety, access to drugs, and burdens on the healthcare delivery system, Congress tasked the agency with "achiev[ing] a somewhat delicate balance of statutory objectives." *Buckman*, 531 U.S. at 348. State laws that, as here, "skew[ ]" this balance, must yield. *Id.* It would be incongruous for Congress to have charged the FDA with achieving that delicate balance only to have it freely overturned as and when States decide to do so.

Legislative Intervenors next argue that there can be no preemption here because in section 355-1, Congress authorized the FDA to impose REMS restrictions only on drug manufacturers, not healthcare providers. Response/Reply Br. 19. As a result, Legislative Intervenors reason, Congress did not intend to regulate the "minutiae" of medical practice in a way that would preempt state law. Response/Reply Br. 1, 6. Legislative Intervenors are correct that drug manufacturers develop and implement REMS requirements. But Congress also gave the FDA the authority to require that REMS impose

specific conditions on the practice of medicine across a range of issues, from how healthcare providers counsel patients, to how they prescribe and dispense medication, to how they monitor patient progress. *See* 21 U.S.C. § 355-1(f)(3). And these regulations are not empty formalities. A REMS may require the "monitor[ing]" and "evaluat[ion]" of how "health care providers, pharmacists, and other parties in the health care system" implement REMS elements. *Id.* § 355-1(f)(4). Thus, as the FDA explains, "[h]ealth care providers with prescribing privileges . . . play a key role in ensuring that products with serious risks requiring REMS are prescribed and used safely."[3] REMS programs may impose any number of requirements on actors across the healthcare delivery system, including on healthcare providers, "such as enrollment in the REMS, completion of training, documentation of counseling of patients, enrollment of patients, monitoring, and/or documentation of compliance with certain safe use conditions." *Id.* In light of this reality, Legislative Intervenors are simply incorrect to suggest that section 355-1 does not regulate healthcare providers.

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[3] U.S. Food & Drug Admin., *Roles of Different Participants in REMS*, bit.ly/4geQFiL (last updated May 7, 2024).

Legislative Intervenors also cite another amendment to the FDCA, codified at 21 U.S.C. § 396, that "expressly disclaims any intent to directly regulate the practice of medicine," *Buckman*, 531 U.S. at 351. Response/Reply Br. 18-19. But again, the relevant text here is section 355-1. And unlike section 396, section 355-1 *does* regulate the practice of medicine by empowering the FDA to impose in a REMS various counseling, prescribing, and monitoring regulations that healthcare providers must follow. 21 U.S.C. § 355-1(f); *see, e.g.*, *Gonzales v. Oregon*, 546 U.S. 243, 270 (2006) (federal statute regulated "medical practice insofar as it bar[red] doctors from using their prescription-writing powers as a means to engage in illicit drug dealing and trafficking as conventionally understood"). The statutory text thus shows that, with respect to a small category of particularly high-risk drugs, Congress sought to give the FDA the kind of "powers in regulating the administration of drugs by the health professions" that ordinarily inhere in the States. *Whalen v. Roe*, 429 U.S. 589, 603 n.30 (1977). Thus, although the presumption against preemption applies in this context, the presumption is overcome on these facts, in light of the

plain text of section 355-1 and the FDA's specific history of mifepristone regulation under the statute.

Lacking support for their position in section 355-1, Legislative Intervenors look beyond the part of the 2007 Amendments that enacted the REMS program. They instead focus on an express preemption provision in a different title of the 2007 Amendments that concerns clinical trial databases. Response/Reply Br. 10 (citing Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801(d), 121 Stat. 823, 922). They suggest that because Congress included an express preemption provision in this one title of the 2007 Amendments, Congress acted intentionally when it did not include an express preemption provision in the different title that enacted section 355-1. Response/Reply Br. 10.

This argument is unpersuasive. It is true that courts may "presume[ ]" that Congress "acts intentionally and purposely" when it "includes particular language in one section of a statute but omits it in another section of the same Act." *Russello v. United States*, 464 U.S. 16, 23 (1983) (citations omitted). But no such presumption holds here. As the Supreme Court has made clear, "[t]he *Russello* presumption—that

the presence of a phrase in one provision and its absence in another reveals Congress' design—grows weaker with each difference in the formulation of the provisions under inspection." *Clay v. United States*, 537 U.S. 522, 532 (2003) (citations omitted). The two provisions here could not be more different. The amendments relating to clinical trials expanded a requirement that certain information on clinical trials be recorded in a public database. Pub. L. No. 110-85, § 801(a), 121 Stat. 823, 922 (codified at 42 U.S.C. § 282(j)(2)). The REMS provisions, by contrast, regulate the use of drugs outside the clinical-trial context.

In any event, as the Supreme Court has also repeatedly made clear, the lack of an express preemption provision does not foreclose a finding of obstacle preemption. AG Opening/Response Br. 48-50. Legislative Intervenors disagree with this line of Supreme Court precedent, Opening Br. 19, but that precedent is binding here.

Legislative Intervenors finally reprise their reliance on the savings clause of the 1962 amendments to the FDCA. They insist that the savings clause is "at a minimum" "relevant" to the analysis. Response/Reply Br. 9. If that savings clause actually applied here, Legislative Intervenors would be right. But Legislative Intervenors

never explain how, based on the text of that provision, the 1962 savings clause *could* possibly apply to the 2007 Amendments. The 1962 savings clause states that "[n]othing in the amendments made by *this Act*"—that is, the 1962 amendments—invalidates "any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict." Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (emphasis added). Thus, by its plain terms, the savings clause does not apply to the 2007 Amendments at issue here.

III. Application of These Longstanding Preemption Principles Will Not Unduly Displace State Laws.

Legislative Intervenors argue that finding preemption here could imperil a swath of other state laws. That fear is unfounded.

To begin, finding preemption here would not mean that "any additional state regulation on a REMS drug" would also fall. Response/Reply Br. 19. Rather, only those state laws that affirmatively conflict with the choices that the FDA has made to balance safety and access through a particular drug's REMS are preempted.

As a result, if this Court were to accept the Attorney General's position, dozens of state opioids laws would not automatically be

preempted. Response/Reply Br. 21-23. The opioid REMS are an entirely distinct regulatory framework from the mifepristone REMS. Therefore, when analyzing whether any state laws governing opioids would be preempted, those state laws must be measured against the federal government's specific regulatory history *for opioids*. And that regulatory history makes crystal-clear that the opioids REMS are "one strategy among multiple national and state efforts to reduce the risk of abuse, misuse, and deaths due to prescription opioid analgesics."[4]

Moreover, a straightforward application of the obstacle-preemption test shows that state opioids laws do not reimpose restrictions that were considered and rejected by the FDA.

Take the North Carolina statute that Legislative Intervenors highlight as an example. Response/Reply Br. 21-22. That statute prohibits a practitioner from prescribing more than a five-day supply of opioids "upon the *initial consultation and treatment* of a patient for acute pain," or a seven-day supply immediately following a surgical procedure. N.C. Gen. Stat. § 90-106(a3) (emphasis added). Legislative

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[4] U.S. Food & Drug Admin., *Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)*, bit.ly/3ZYAsIJ (last accessed Dec. 7, 2024).

Intervenors suggest that this statute would be preempted under the Attorney General's theory because the FDA has considered and rejected implementing a general duration limit. Response/Reply Br. 21. Not so. The state law only limits the *initial* prescription of opioids—it does not stop a prescriber from issuing "any appropriate renewal, refill, or new prescription." N.C. Gen. Stat. § 90-106(a3). It, too, does not implement a general duration limit. Accordingly, the state law does not reimpose a condition that the FDA has considered and rejected.

But even if the state law did restrict the overall duration of use for any opioid, Legislative Intervenors' description of the FDA's position based on a 2013 response to a citizen petition is still inaccurate. The response states that "more data are needed regarding . . . the relationship between opioid duration of use and adverse effects, before the Agency can determine whether additional action needs to be taken."[5] Rather than considering and rejecting a limitation on the duration of use, the FDA explicitly left open the possibility that

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[5] Letter from J. Woodcock to A. Kolodny, Re: Docket No. FDA-2012-P-0818 (Sept. 10, 2013), *available at* https://perma.cc/RK2J-HTAH (last accessed Dec. 10, 2024).

additional actions might need to be taken. In that way, the FDA's response fell entirely in line with its general approach of requiring that the opioid REMS coexist with any additional federal and state restrictions.

The same can be said for the FDA's consideration of a maximum daily dose. Legislative Intervenors raise the fear that state laws that include a maximum-dose limit will automatically fall. Response/Reply Br. 22-23. But the FDA has never considered and rejected the inclusion of a maximum dose limit. Instead, like its position on a limitation on duration of use, the FDA has explicitly held open the need for further study to determine whether additional actions might be required.[6] And, pursuant to that further study, the FDA did indeed include in its guidance to healthcare providers that they consider "[d]osing instructions including daily maximum" when they prescribe opioids.[7] Far from considering and rejecting a daily maximum, the FDA has

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6 *Id.*

7 U.S. Food & Drug Admin., *FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* (Sept. 2018), bit.ly/3BD3UL8 (last accessed Dec. 10, 2024).

demonstrated its openness to providers, other agencies, and states stepping in with these limitations.

Legislative Intervenors also claim that if Dr. Bryant were to prevail here, this Court would be "blue pencil[ing] dozens of different state laws." Response/Reply Br. 20 (citing dozens of statutes requiring some form of informed consent or waiting periods). This concern is unfounded. Take, as an example, the bevy of "waiting period" laws that Legislative Intervenors worry would automatically fall if the North Carolina waiting-period law were preempted. *Id.* at 20, 34-35. Before another State's waiting-period law would be preempted, a court would have to first hold that the FDA has affirmatively adopted and rescinded a REMS requirement that implements *that* state law. That analysis may differ depending on whether, for example, the state law requires the waiting period after an in-person appointment (like North Carolina's law requires) or whether that waiting period applies to surgical abortions and not medication abortions. Without consideration of those factors, it is wrong to assume that such laws would be preempted. Thus, in the vast majority of circumstances—including in

state regulation of opioids—state laws and REMS restrictions can and do coexist.

CONCLUSION

Attorney General Stein respectfully requests that this Court affirm in part and reverse in part the district court's judgment.

Respectfully submitted,

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December 18, 2024

CERTIFICATE OF COMPLIANCE

I certify that this brief complies with the type-volume limitations of Fed. R. App. P. 28.1(e)(2)(C) because it contains 4,915 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f). This brief complies with the typeface and type-style requirements of Fed. R. App. P. 32(a)(5) & (6) because it has been prepared in a proportionally spaced typeface: 14-point Century Schoolbook font.

Respectfully submitted, this the 18th day of December 2024.

/s/ Sripriya Narasimhan
Sripriya Narasimhan

CERTIFICATE OF SERVICE

I certify that on December 18, 2024, I filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Fourth Circuit by using the appellate CM/ECF system. Participants in the case are registered CM/ECF users and service will be accomplished by the appellate CM/ECF system.

Respectfully submitted, this the 18th day of December 2024.

/s/ Sripriya Narasimhan
Sripriya Narasimhan