FDA LEADS, STATES MUST FOLLOW

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ABSTRACT

Courts have long deferred to the FDA's scientific expertise, particularly on matters of drug safety and effectiveness. But now, in the aftermath of the U.S. Supreme Court's unraveling of deference to administrative agencies, coupled with its relegation of abortion to elected officials, the FDA faces a ratcheting up of two distinct types of legal challenges: (1) direct challenges to FDA actions, including abortion (and other) drug approval decisions, and (2) indirect challenges to the primacy of FDA actions that arise in the context of preemption disputes over the extent to which state regulations conflict with federal regulatory schemes. Direct challenges to FDA actions are relatively rare and almost never succeed. Indirect challenges posed by state bans or restrictions on FDA-approved drugs amount to a new preemption frontier facing courts.

Where Congress has not definitely addressed the federal-state regulatory interaction, this Article marshals the longstanding record of judicial deference to the FDA's scientific expertise; the "agency reference model" supported by existing implied preemption doctrine; principles embedded in the statutes and regulations governing FDA approval of drugs; and normative arguments about the need for national uniformity to build a novel preemption framework to be enforced by courts in which the FDA's risk calculus leads and the states must follow.

Under our framework, states cannot ban FDA-approved drugs, whether due to health and safety concerns or political or moral objections. State restrictions that subvert the FDA's risk calculus, such as bans of abortion-inducing drugs or telehealth proscriptions, cannot withstand preemption. But, where the FDA has not acted, states can fill the void either with gap-filling drug safety regulation, or—as the proliferation of gender-affirming care bans forewarns—the bootstrapping of politically motivated decisions under the guise of health and safety concerns.

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Our framework, whereby the FDA leads and states must follow, not only promotes national regulatory uniformity but—equally significantly—it harnesses the FDA's capacity to incentivize the generation of high-quality clinical data about drugs' safety and effectiveness.

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INTRODUCTION

How has the federal Food and Drug Administration (FDA) emerged front and center in some of the most divisive current political debates over abortion? To what extent should we widen our collective legal lens to embrace the protections and staying power of administrative law principles in spheres that intersect with health and safety? We take up each of these questions in this Article, which proposes a novel framework that courts can use to resolve various kinds of legal challenges to FDA actions.

The FDA approved the abortion drug mifepristone (brand name Mifeprex) in 2000 and, in subsequent years, took actions to expand access to the drug, allowing it to be sold at retail pharmacies, to be dispensed by mail, and to be prescribed by non-physicians.[1] In November, 2022, anti-abortion doctors and medical associations sued the FDA, arguing that its approval of mifepristone in 2000 was flawed and that the subsequent changes to its distribution and use lacked scientific evidence.[2] The federal district court agreed with the plaintiffs and "enjoined FDA's approval of mifepristone, thereby ordering mifepristone off the market."[3] (The U.S. Supreme Court then stayed this order pending resolution of appeals.) The Fifth Circuit reined in the district court's order, vacating it with regard to the 2000 approval of the drug, but affirming with regard to the FDA's subsequent loosening of regulatory restrictions.[4] Last Term, in *FDA v. Alliance for Hippocratic Medicine*, the U.S. Supreme Court stopped this particular case in its tracks, dismissing for lack of standing, but leaving the door open for other challenges and a future decision on the merits.[5]

The stakes are high. Medication abortion is the most common form of abortion in the United States.[6] Anti-abortion and pro-abortion rights activists alike consider medication abortion the next significant legal

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1. *See Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation*, FDA (Sept. 1, 2023) [hereinafter *Questions and Answers on Mifepristone*], https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation [https://perma.cc/HH5Q-WAFA]; *see also Approval Package for Application Number 020687Orig1s025*, CTR. FOR DRUG EVALUATION & RSCH. (Jan. 3, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/020687Orig1s025.pdf [https://perma.cc/C6KD-Q2JM].

2. *See* Brendan Pierson, *Anti-Abortion Groups Ask U.S. Court to Pull Approval for Abortion Drugs*, REUTERS (Nov. 18, 2022, 3:46 PM), https://www.reuters.com/legal/anti-abortion-groups-ask-us-court-pull-approval-abortion-drugs-2022-11-18 [https://perma.cc/8LPY-CG8M].

3. FDA v. All. for Hippocratic Med., 602 U.S. 367, 377 (2024) (citing 668 F. Supp. 3d 507 (N.D. Tex. 2023)).

4. *See id.*

5. *See id.* at 396 ("Here, the plaintiffs have failed to demonstrate that FDA's relaxed regulatory requirements likely would cause them to suffer an injury in fact."); *id.* ("[I]t is not clear that no one else would have standing to challenge FDA's relaxed regulation of mifepristone.").

6. *See* Rachel K. Jones, Elizabeth Nash, Lauren Cross, Jesse Philbin & Marielle Kirstein, *Medication Abortion Now Accounts for More than Half of All US Abortions*, GUTTMACHER INST. (Dec. 1, 2022), https://www.guttmacher.org/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions [https://perma.cc/VKW4-WUJH]; Joanna Grossman & Nathan Cortez, *Who Regulates Abortion Now?*, 110 IOWA L. REV. (forthcoming 2025) (arguing that, since medication abortion accounts for most abortions, abortion is as much a matter of federal regulation as state, and that federal regulation is better aimed at achieving what patients want out of medicine).

frontier of the abortion debate since the U.S. Supreme Court overturned *Roe v. Wade*[7] in *Dobbs*.[8]

Meanwhile, states have taken matters into their own hands, enacting laws that ban or restrict abortion generally, or medication abortion in particular.[9] Challenges to some of these laws are working their way through the federal courts.[10] Preemption might provide a powerful weapon against such laws, but courts are in search of a framework to provide guidance on how to resolve these state-FDA conflicts.

Drawing on the insight that all of these cases implicate deference to the scientific expertise of the FDA and taking up the administrative law mantle—an angle that has been overshadowed by the political and ideological debates surrounding abortion—this Article proposes a framework to evaluate two distinct types of legal challenges: (1) direct challenges to FDA actions, including drug approval decisions, and (2) indirect challenges to the primacy of FDA actions that arise in the context of preemption disputes over the extent to which state regulation—in the form of either tort claims or state statutory or regulatory law—conflicts with federal regulatory schemes.

Direct legal challenges to FDA actions, such as administrative law challenges to drug approval decisions, are relatively rare and almost never succeed. As a historical matter, courts have given strong-form deference to the FDA's scientific judgments regarding pharmaceutical drugs and medical devices.[11] In a direct challenge like *Alliance for Hippocratic Medicine*, courts scrutinize FDA decision-making, especially where the FDA has not followed its own protocols or has changed its position without providing justification. But they are apt to acquiesce in the agency's scientific judgments, even as administrative deference doctrines have come under broad attack, including before the U.S. Supreme Court.[12]

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7. 410 U.S. 113 (1973).

8. *See* Abbie VanSickle, *Supreme Court Maintains Broad Access to Abortion Pill Access*, N.Y. TIMES (June 13, 2024), https://www.nytimes.com/2024/06/13/us/politics/supreme-court-abortion-pill-mifepristone-ruling.html [https://perma.cc/Z48H-Z4FR] ("Abortion rights groups cautioned that the ruling only maintained the status quo. 'The anti-abortion movement sees how critical abortion pills are in this post-*Roe* world, and they are hell bent on cutting off access,' Nancy Northup, the president of the Center for Reproductive Rights, said in a statement."); *id.* ("Erin Hawley, senior counsel for Alliance Defending Freedom, the conservative legal organization that represented the plaintiffs, suggested that the case could be revived through three Republican-led states, Idaho, Kansas, and Missouri, which had intervened as plaintiffs at the lower court level.'"); *see also* Dobbs v. Jackson Women's Health Org., 597 U.S. 215 (2022).

9. *See infra* Sections II.C, IV.A.

10. *See infra* Section IV.A.

11. *See infra* Section I.A.

12. *See infra* Section I.B.

Meanwhile, what we term indirect legal challenges to FDA actions have proliferated. In such cases, the FDA is not a direct party to the dispute, typically between private parties, one of whom asks the court to defer or give weight to an action or decision made by the FDA. In this realm, courts grant the FDA a kind of conditional deference, defeasible if—as in the direct challenge context—it has not consistently followed its protocols or has changed its views without providing empirical justification. Moreover, consistent with the "agency reference model," courts scrutinize the regulatory record of the FDA to determine whether the agency has weighed in on the precise risk at issue in the state law tort claims.[13] Where, for example, new risk evidence (not before the FDA at the time of approval) has come to light, state law tort actions can come forward (and are thus not preempted) to force the manufacturer to go back to the FDA with such new risk evidence (and thereby earn preemption).[14]

Attempts by states to ban or restrict FDA-approved drugs are the next preemption frontier. In 2019, the FDA approved GenBioPro's generic version of mifepristone. In 2023, GenBioPro sued the state of West Virginia over its abortion restrictions, arguing that federal regulations authorizing the use of mifepristone should prevail over West Virginia's laws.[15] Such indirect challenges to FDA actions implicate clashes between state and federal interests in spheres of concurrent state and federal authority: the practice of medicine and abortion.

This next frontier calls out for a new preemption framework. To date, scholars have approached this issue as a clash of antagonistic "dual sovereigns," requiring either new legislation to expressly preempt state restrictions,[16] or renewed assertions by the FDA of its preemptive regulatory

13. *See* Catherine M. Sharkey, *Federalism Accountability: "Agency-Forcing" Measures*, 58 DUKE L.J. 2125, 2153 (2009) [hereinafter *Federalism Accountability*] (promoting "an 'agency reference model' that 'directs attention to a repository of agency information . . . focusing on the precise nature of the agency's regulatory cost-benefit (or risk-risk) determinations as well as the economic consequences of various determinations and the effects of state regulation on federal regulatory schemes'" (quoting Catherine M. Sharkey, *Products Liability Preemption: An Institutional Approach*, 76 GEO. WASH. L. REV. 449, 485 (2008) [hereinafter *Products Liability Preemption*])); *see also infra* Section III.C (discussing the agency reference framework).

14. *See infra* Section II.B.

15. *See* GenBioPro, Inc. v. Sorsaia, No. 3:23-0058, 2023 WL 5490179, at *3 (S.D.W. Va. Aug. 24, 2023).

16. *See* Allison M. Whelan, *Aggravating Inequalities: State Regulation of Abortion and Contraception*, 46 HARV. J.L. & GENDER 131, 198–201 (2023) (recommending, as the "ideal solution," "amending the FDCA to include an express preemption provision specific to pharmaceutical bans and restrictions").

authority.[17] Our approach instead starts with the assumption that the states and federal government share *concurrent* authority to regulate both abortion and the practice of medicine.[18] Where Congress has not definitely addressed the federal-state regulatory interaction, this Article marshals the longstanding record of judicial deference to the FDA's scientific expertise; the "agency reference model" supported by existing implied preemption doctrine; principles embedded in the statutes and regulations governing FDA approval of drugs; and normative arguments about the need for national uniformity to build a novel preemption framework to be enforced by *courts* in which the FDA's risk calculus *leads* and the states must *follow*.

Part I addresses direct legal challenges to FDA actions, implicating administrative, statutory, and constitutional grounds. The historical trend of longstanding deference to the FDA's scientific expertise when directly challenged puts in sharp relief the scientific second-guessing that the lower courts did in *Alliance for Hippocratic Medicine*.

Part II moves from direct to indirect legal challenges to the FDA's authority, with consideration of both the preemption defense to products liability actions and state positive laws that contradict FDA actions. Here, we draw upon some historical analogs, which highlight how preemption doctrine has not yet adapted to address attempts by states to ban or restrict FDA-approved pharmaceuticals.

Part III moves from the descriptive to prescriptive, mapping out how courts should apply our novel framework. We critique the prevailing approaches that scholars have put forward and instead extend the agency reference model to argue that only state restrictions that complement federal restrictions and that help guarantee the safety and effectiveness of drugs should withstand preemption challenges. States must not be allowed to ban drugs that the FDA has approved, including mifepristone, whether due to health and safety concerns or political or moral objections.

Part IV applies our framework to state restrictions on medication abortion. Under our approach, restrictions that subvert the FDA's risk calculus, such as bans of abortion-inducing drugs or telehealth proscriptions, cannot withstand preemption. But, where the FDA has not acted, states can fill the void either with gap-filling drug safety regulation,

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17. *See id.* at 201–03 (recommending as the "second-best" solution non-legislative ways for the FDA to "clarify the preemptive effect of FDA approval" including new regulations, guidance documents, policy statements, and public statements); *cf.* David S. Cohen, Greer Donley & Rachel Rebouché, *Abortion Pills*, 76 STAN. L. REV. 317, 370–76 (2024) (recommending steps that the FDA and abortion rights advocates could take to promote access to medication abortion, such as eliminating the mifepristone REMS, bringing procedural challenges to further restrictions, and approving mifepristone for multiple uses).

18. *See infra* Part III.

or—as the proliferation of gender-affirming care bans forewarns—the bootstrapping of politically motivated decisions under the guise of health and safety concerns.

I. DIRECT CHALLENGES

Direct legal challenges to the FDA's actions regarding health and safety—including drug approval decisions—are relatively rare. Historically, courts have deferred to the agency's scientific expertise when such actions are challenged on procedural, statutory, or constitutional grounds. Thus the FDA is poised to withstand waning deference to federal agencies in general and challenges to its approval of medication abortion pills in particular.

A. Historical Trend of Deference

Courts have consistently deferred to the FDA's scientific expertise, particularly on matters related to drug approval. They have shown little appetite for second-guessing such scientific judgments in administrative law challenges, unless procedural irregularities or inconsistencies plague FDA actions. Even so, such procedural deficiencies tend not to be based on the agency's error of *scientific judgment*; rather, they are based on the agency's failure to *explain* its scientific judgment.

1. Procedural Challenges

Courts have been particularly deferential to FDA decisions to approve or disapprove drugs and medical devices on safety and effectiveness grounds.[19] For example, the D.C. Circuit rejected an arbitrary and capricious challenge under the Administrative Procedure Act (APA)[20] to the FDA's decision not to approve a prescription opioid with a proposed label

19. A new drug cannot enter the national market until the FDA has approved its application. *See* 21 U.S.C. § 355(a). The FDA can only approve a new drug if it finds substantial evidence that the drug is safe and effective for its intended use. *See id.* § 355(d). Moreover, it can approve a generic drug that is the bioequivalent of a drug it has already approved as safe and effective for its intended use. *See id.* § 355(j).

20. Courts review agency actions to determine whether they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). Under the *State Farm* framework, an agency rule is arbitrary and capricious if the agency makes its determination based on factors Congress did not intend it to consider; fails to address an important aspect of the problem; explains its decision in a way contrary to the evidence before it; or offers an explanation so implausible that it could not be the product of agency expertise. *See* Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983).

describing the drug as "abuse deterrent."[21] The FDA examined the evidence that the drug's manufacturer put forward and concluded it did not show that the drug would in fact deter abuse.[22] The court was especially wary of second-guessing the FDA's expertise.[23] It warned against "step[ping] into the FDA's shoes and reassess[ing] its scientific judgments—a role [courts] are 'ill-equipped' to play 'under the guise of the APA's arbitrary and capricious standard.'"[24] The court liberally quoted another opinion authored by then-Judge Kavanaugh, in which the D.C. Circuit deferred to the FDA's scientific judgment by rejecting a challenge to the agency's determination that a medical device was not "substantially equivalent" to others currently on the market.[25]

Plaintiffs who have challenged more technical FDA determinations on arbitrary and capricious grounds have typically fared no better. For example, the D.C. district court rejected a procedural challenge to the FDA's decision not to approve one manufacturer's drug application because it gave *Chevron* deference[26] to the agency's interpretation of what constituted a "protein."[27] The court emphasized that the agency had

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21. *See* Pharm. Mfg. Rsch. Servs., Inc. v. FDA, 957 F.3d 254, 257 (D.C. Cir. 2020); *see id.* (noting that any manufacturer seeking FDA approval to market a drug as "abuse deterrent" must establish "substantial evidence that the drug will have the effect . . . suggested in the proposed labeling thereof" (quoting 21 U.S.C. § 355(d))).

22. *Id.* at 262–63 (finding no support for the manufacturer's claims that a special dye would deter abuse; that the drug had increased resistance to extraction compared to another FDA-approved drug; or that the drug would deter abuse by snorting).

23. *See id.* at 262 (noting that when the FDA's decision-making is challenged, courts must give a "high level of deference" to the agency's analysis of the scientific evidence before it (citing Rempfer v. Sharfstein, 583 F.3d 860, 867 (D.C. Cir. 2009))); Cytori Therapeutics, Inc. v. FDA, 715 F.3d 922, 923 (D.C. Cir. 2013) (Kavanaugh, J.) (evincing wariness of "unduly second-guess[ing] an agency's scientific judgments" in the context of an arbitrary and capricious challenge to an FDA decision relating to a medical device).

24. *See Pharm. Mfg. Rsch. Servs.*, 957 F.3d at 265 (quoting *Cytori Therapeutics*, 715 F.3d at 927).

25. *See Cytori Therapeutics*, 715 F.3d at 924–25. Under the Medical Device Amendments (MDA) to the FDCA, if the FDA determines that a medical device is substantially equivalent to a device that exists on the market, it goes through a more streamlined approval process. *See id.* at 923 (citing 21 U.S.C. §§ 360(k), 360c(i)).

26. *Chevron* established a two-step framework in which courts first determine whether a statute is silent or ambiguous on an issue, and then, if so, defer to the agency's reasonable interpretation of it. *See* Chevron U.S.A. Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837, 842–44 (1984). The U.S. Supreme Court recently overruled *Chevron*. *See* Loper Bright Ents. v. Raimondo, 144 S. Ct. 2244, 2273 (2024). We discuss its likely impact on deference to the FDA's scientific judgments *infra* Section I.B.

27. Teva Pharms. USA, Inc. v. FDA, 514 F. Supp. 3d 66, 98, 100–03 (D.D.C. 2020). Indeed, this case is Exhibit A in Justice Kagan's dissent in *Loper Bright*:

> Under the Public Health Service Act, the [FDA] regulates "biological product[s]," including "protein[s]." . . . When does an alpha amino acid polymer qualify as such a "protein"? Must it have a specific, defined sequence of amino acids? (citing *Teva*, 514 F. Supp. 3d at 79–80, 93–106). . . . When does an alpha amino acid polymer qualify as a "protein"? . . . I don't know

"developed [its definition] after convening a working group of experts to analyze the term 'protein,' surveying the relevant scientific literature, considering various scientific, regulatory, and statutory factors, and engaging with the regulated industry for nearly a decade."[28] The court characterized the FDA's analytical process as "rational, and, in light of the broad scientific agreement . . . so too is the definition it produced."[29] Furthermore, it rejected the manufacturer's contention that the FDA treated its drug inconsistently (and thus, arbitrarily) compared to other drugs approved by the agency. The court justified such deference by noting that courts are ill-equipped to second-guess the FDA's scientific judgments under the guise of arbitrary and capricious review.[30] Courts have consistently reached similar conclusions based on deference to the FDA's scientific expertise.[31]

Even when courts find the FDA's decisions procedurally deficient, they tend not to second-guess the agency's scientific expertise. In other words, the noted procedural deficiencies tend not to be based on an agency's error of *scientific judgment*; rather, they are based on the agency's failure to *explain* its scientific judgment. *Braeburn Inc. v. FDA*[32] provides a vivid illustration. The D.C. district court was called upon to determine whether the FDA could bar final approval of plaintiff's pharmaceutical drug (Brixadi Monthly) on the grounds that such approval would be for the "conditions of approval," and thus violate its competitor's (Sublocade) right to

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> many judges who would feel confident resolving that issue. (First question: What even is an alpha amino acid polymer?) But the FDA likely has scores of scientists on staff who can think intelligently about it, maybe collaborate with each other on its finer points, and arrive at a sensible answer.

Loper Bright, 144 S. Ct. at 2296–98 (Kagan, J., dissenting) (citations omitted).

28. *Teva*, 514 F. Supp. 3d at 102.

29. *Id.* at 103.

30. *Id.* at 106–09.

31. *See, e.g.*, Henley v. FDA, 77 F.3d 616, 621 (2d Cir. 1996) ("The FDA possesses the requisite know-how to conduct . . . analyses [about the link between oral contraceptives and cancer based on animal studies], by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug, and how those data affect human usage. We therefore defer to its reasonable findings in this case."); Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 219–20 (D.D.C. 1996) (deferring to the FDA's decision to rely on in vitro testing data to approve a generic drug because "parties' dispute is fundamentally a scientific one over which the court lacks expertise and over which the FDA is the expert"); Berlex Lab'ys, Inc. v. FDA, 942 F. Supp. 19, 25 (D.D.C. 1996) (concluding that the FDA's reliance on certain clinical trials was a reasonable interpretation of the agency's regulations as the "FDA's policies and its interpretation of its own regulations will be paid special deference because of the breadth of Congress' delegation of authority to FDA and because of FDA's scientific expertise"); Ipsen Biopharmaceuticals, Inc. v. Becerra, 678 F. Supp. 3d 20, 38–40 (D.D.C. 2023) (deciding that the dispute over whether a particular product was a "protein" was a scientific one, requiring the court to be deferential to the FDA's scientific determination).

32. 389 F. Supp. 3d 1 (D.D.C. 2019).

exclusivity.[33] The court withheld *Chevron* deference from the FDA's interpretation of "conditions of approval" because the agency "fail[ed] to supply a standard by which a drug's innovation is defined."[34] The court conceded that the FDA exercised "a degree of scientific judgment" which was partly "appropriate[]," but took the agency to task for failing to "*explain* the standard . . . that informs how the innovation against which those differences are judged is defined."[35] The court, moreover, determined that the FDA did not consistently apply its definition of "innovation," making its determination arbitrary and capricious in violation of the APA.[36] Accordingly, it vacated the FDA's decision letter.[37] Such errors of consistency[38]—and highly technical decisions related to patents[39]—are at the core of the rare successful arbitrary and capricious challenges to the FDA's decisions that have joined *Braeburn*'s ranks.

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33. *Id.* at 20. Under the so-called bar clause of the relevant provision, the FDA cannot "make the approval of an application . . . for the conditions of approval of [an exclusivity-eligible pharmaceutical product] effective before the expiration of three years from the date of the approval of the [exclusivity eligible pharmaceutical product]." 21 U.S.C. § 355(c)(3)(E)(iii). Whether an already-approved pharmaceutical product bars final approval of a later product depends on the overlap between "the conditions of approval" of the two products. *Braeburn*, 389 F. Supp. 3d at 20.

34. *Braeburn*, 389 F. Supp. 3d at 27.

35. *Id.* at 26 (emphasis added).

36. *See id.* at 29–30.

37. *See id.* at 30.

38. *See, e.g.*, Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 28 (D.D.C. 1997) (concluding that the FDA is not free "to permit two sets of similar products to run down two separate tracks, one more treacherous than the other, for no apparent reason" as this is "the essence of the meaning of arbitrary and capricious"); Genus Med. Techs., LLC v. FDA, 994 F.3d 631, 644 (D.C. Cir. 2021) (finding that the FDA's decision to classify diagnostic contrast agent as a drug rather than a device "must be set aside because it was based on an erroneous interpretation" of the FDCA); *id.* at 643–44 (stressing that "the FDA did not invoke its expertise" and "emphasiz[ing] the purely legal nature of the question before [the court]"); Teva Pharms. USA, Inc. v. Sebelius, 595 F.3d 1303, 1318 (D.C. Cir. 2010) (rejecting "the interpretation of the statute that the FDA has adopted in two recent adjudications"); Zotos Int'l, Inc. v. Young, 830 F.2d 350, 353–54 (D.C. Cir. 1987) (finding the FDA's decision to deny applicant's trade secret status for a cosmetic ingredient was arbitrary and capricious because it was ill-explained, but noting that "it would be most difficult for [the court] to find the FDA's rejection of [the applicant's] arguments arbitrary if the parties' dispute were only a scientific one"); Rhodia, Inc. v. FDA, 608 F.2d 1376, 1379 (D.C. Cir. 1979) (finding the FDA's decision to deny a supplemental drug application on the grounds that an additional supplier would increase the quantity of the drug on the market to be arbitrary and capricious "[i]n view of its previous course, bypassing quantity as a determinative criterion").

39. *See, e.g.*, Am. Bioscience, Inc. v. Thompson, 269 F.3d 1077, 1086 (D.C. Cir. 2001) (finding that the FDA had acted arbitrarily and capriciously when it approved a generic drug application without following the proper patent-related procedures); *id.* at 1079 ("This dispute arises out of the complex relationship between the FDA's approval process for generic drugs and patent law."); Teva Pharms. USA, Inc. v. FDA, 441 F.3d 1, 5 (D.C. Cir. 2006) (finding arbitrary and capricious the FDA's finding that a generic drug manufacturer's voluntary dismissal of a declaratory judgment action against a patentee was a binding court decision); Purepac Pharm. Co. v. Thompson, 354 F.3d 877, 883–84 (D.C. Cir. 2004) (finding that the FDA's decision that a patent covered a certain drug's use for epilepsy was "the height of arbitrary and capricious decision making").

2. Statutory and Constitutional Challenges

The U.S. Supreme Court has invoked, for decades, some version of the "major questions" administrative law doctrine to clip the wings of federal agencies that push the boundaries of their regulatory authority.[40] The FDA has largely avoided scrutiny relative to other agencies, likely because the FDA's regulatory interests are often aligned with the business interests of drug and device manufacturers.[41] Indeed, *Brown & Williamson*[42]—rejecting the FDA's attempt to regulate tobacco products—is the only major questions challenge[43] to the FDA's authority of any note. (Thereafter,

40. The major questions doctrine (broadly construed) prohibits federal agencies from taking large-scale actions without specific congressional authorization. *See* MCI Telecomms. Corp. v. Am. Tel. & Tel. Co., 512 U.S. 218 (1994) (rejecting the FCC's attempt to waive a tariff requirement under its authority to "modify any requirement"); Whitman v. Am. Trucking Ass'ns, 531 U.S. 457 (2001) (rejecting the EPA Administrator's authority to consider implementation costs when setting national air quality standards); Util. Air Regul. Grp. v. EPA, 573 U.S. 302, 324 (2014) (rejecting the EPA's attempt to construe the term "air pollutant" to cover greenhouse gases, which would "require permits for the construction and modification of tens of thousands, and the operation of millions, of small sources nationwide"); Ala. Ass'n of Realtors v. Dep't of Health & Hum. Servs., 594 U.S. 758 (2021) (per curiam) (rejecting the CDC's nationwide eviction moratorium, which Congress would have to specifically authorize). With *West Virginia v. EPA*, 597 U.S. 697 (2022), the Court has "reinvigorated" this doctrine. *See infra* Section I.B.1; *see also* Peter M. Shane, *This Will Be a Big Year for the Roberts Court's Major Questions Doctrine*, WASH. MONTHLY (Feb. 27, 2024), https://washingtonmonthly.com/2024/02/27/this-will-be-a-big-year-for-the-roberts-courts-major-questions-doctrine [https://perma.cc/V263-977C] (arguing that the Roberts Court "has formulated an anti-regulatory 'major questions doctrine' (MQD) to limit agency initiative").

41. *See* Brief for the Pharmaceutical Research and Manufacturers of America as *Amicus Curiae* in Support of Petitioners, FDA v. All. for Hippocratic Med., 602 U.S. 367 (2024) (Nos. 23-235 & 23-236) (arguing that the Supreme Court should grant certiorari in the challenge to the FDA's actions on mifepristone because the Fifth Circuit's decision threatens to disrupt the pharmaceutical industry and discourage innovation); Press Release, Pharm. Rsch. & Mfrs. of Am. (PhRMA), PhRMA Statement on the FDA and Latest U.S. Supreme Court Decision (Apr. 21, 2023), https://phrma.org/en/resource-center/Topics/Access-to-Medicines/PhRMA-Statement-on-the-FDA-and-Latest-US-Supreme-Court-Decision [https://perma.cc/Q9G3-5YVS] ("Congress gave the FDA the authority to determine whether a medicine is safe and effective for patients to use. Allowing the courts to second-guess a decision by the FDA to approve a medicine would create significant uncertainty and harm for manufacturers, patients and physicians."); Katrina Megget, *PhRMA Stands by Federal Preemption in Wyeth/Levine Case*, PHARMATIMES (Nov. 4, 2008), https://pharmatimes.com/news/phrma_stands_by_federal_preemption_in_wyethlevine_case_986455 [https://perma.cc/YQ5B-G44E] (quoting PhRMA senior vice president Ken Johnson as saying that "[f]ederal preemption, at its heart, is about protecting patients through nationally uniform and scientifically based warnings on prescription drug labels").

42. FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 159–60 (2000) (finding the FDA could not regulate tobacco products as medical devices or drugs because Congress created a distinct regulatory scheme for them); *see also id.* at 127 ("The FDA determined that nicotine is a 'drug' and that cigarettes and smokeless tobacco are 'drug delivery devices,' and therefore it had jurisdiction under the FDCA to regulate tobacco products as customarily marketed . . . .").

43. Although the phrase "major questions doctrine" was not coined at the time of *Brown & Williamson*, the Court has since described it as a "major questions" case. *See West Virginia*, 597 U.S. at 723–24.

Congress passed the Tobacco Control Act, specifically authorizing the FDA to regulate tobacco products.[44])

Outside the realm of pharmaceutical drugs and medical devices, manufacturers and other actors in the dietary supplement and tobacco industries have challenged FDA regulations on the grounds that the agency has exceeded its statutory or constitutional authority. These actors are financially incentivized to oppose FDA regulations, which can pose existential threats to their businesses. The majority of courts have been unwilling to invalidate FDA regulations or statutory provisions that empower the agency to regulate dietary supplements.[45] And, although some courts have recently made some noise about the FDA's treatment of particular vaping companies and products,[46] *Nicopure Labs, LLC v. FDA* showcases the historical deference they have accorded to the agency's underlying scientific judgments.[47] In that case, the D.C. Circuit rejected an arbitrary and capricious challenge to the FDA's decision to regulate e-cigarettes as a "modified risk tobacco product," which requires heightened premarket authorization standards under the Tobacco Control Act.[48] The court was persuaded that the FDA's final rule "cited to a robust body of scientific evidence about the uses and risks of e-cigarettes and explained in detail how the evidence informed the agency's decision to subject them to the Act's requirements."[49]

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44. *See* Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, 123 Stat. 1776 (2009) (codified as amended at 21 U.S.C. §§ 387–387u).

45. Dietary supplement manufacturers have brought largely unsuccessful constitutional challenges to FDA regulations. *See* All. for Nat. Health U.S. v. Sebelius, 775 F. Supp. 2d 114, 132–33 (D.D.C. 2011) (rejecting challenge that the FDA's dietary supplement regulations were unconstitutionally vague because they contained terms like "adequate," "appropriate," "suitable," and "qualified"); Nutritional Health All. v. Shalala, 144 F.3d 220, 223, 227–28 (2d Cir. 1998) (rejecting plaintiff's claim that the FDA's supplement labeling requirements regarding "emerging health claims" amounted to an unconstitutional prior restraint of commercial speech); *cf.* Nutritional Health All. v. FDA, 318 F.3d 92, 100–01 (2d Cir. 2003) (invalidating an FDA regulation requiring that manufacturers containing 30 mg or more of iron per dosage distribute the products in single-unit packages—aimed at preventing iron poisoning—because the FDCA's adulteration provisions only authorize the FDA to regulate a product according to how it is meant to be used, not misused).

46. *See, e.g.*, Wages & White Lion Invs. v. FDA, 90 F.4th 357, 371 (5th Cir. 2024) (en banc) (finding that the FDA acted arbitrarily when it rejected petitioners' premarket tobacco applications (PMTAs) after the agency changed its position on various requirements); Bidi Vapor L.L.C. v. FDA, 47 F.4th 1191, 1195 (11th Cir. 2022) (finding that the FDA's failure to consider companies' "marketing and sales-access-restriction plans designed to minimize youth exposure and access" to their electronic vaping products was arbitrary and capricious); *see also* Jonathan H. Adler, *The Food & Drug Administration Has a Vaping Problem*, VOLOKH CONSPIRACY (July 8, 2022, 8:05 AM), https://reason.com/volokh/2022/07/08/the-food-drug-administration-has-a-vaping-problem [https://perma.cc/6CKT-ZUY9] (arguing that the FDA has "time and again flouted basic administrative law requirements in denying PMTAs from vaping companies").

47. 944 F.3d 267, 281–82 (D.C. Cir. 2019).

48. *Id.* at 282–84.

49. *Id.* at 273.

B. Reinvigorated Challenges

Recent developments in administrative and constitutional law could upend the historical trend of judicial deference to the agency's safety and effectiveness determinations. The U.S. Supreme Court's one-two punch of *West Virginia v. EPA*[50] (reinvigorating the major questions doctrine) and *Dobbs*[51] (overturning the right to abortion) could make the FDA's actions on medication abortion pills ripe for direct challenges under the "major questions" doctrine of administrative law. Adding salt to the wound, the Court overruled *Chevron*, a "cornerstone of administrative law" that accorded deference to agency statutory interpretations, in *Loper Bright Enterprises v. Raimondo*.[52] It is against this backdrop that *Alliance for Hippocratic Medicine* landed at the Supreme Court; though the Court left for another day resolution of any arbitrary and capricious challenge to the FDA's actions on mifepristone.

1. The Shifting Administrative Law Landscape

The "major questions" doctrine was reinvigorated by the U.S. Supreme Court in *West Virginia v. EPA*.[53] The Court held that federal agencies must point to "clear congressional authorization" in "extraordinary cases" in which the agency is "asserting highly consequential power beyond what Congress could reasonably be understood to have granted."[54] More recently, the Court overruled *Chevron*, reasoning that "[t]he deference that *Chevron*

50. 597 U.S. 697, 723–24 (2022) (holding that where an agency asserts authority of extraordinary history and breadth or great economic and political significance, courts should hesitate before concluding that Congress conferred that authority because the agency must point to clear congressional authorization for the power it claims).

51. Dobbs v. Jackson Women's Health Org., 597 U.S. 215, 231 (2022) (overruling *Roe* and *Casey*).

52. *See* Loper Bright Ents. v. Raimondo, 144 S. Ct. 2244, 2273 (2024) ("*Chevron* is overruled. . . . [C]ourts need not and under the [Administrative Procedure Act] may not defer to an agency interpretation of the law simply because a statute is ambiguous."); *id.* at 2294 (Kagan, J., dissenting) ("For 40 years, [*Chevron*] has served as a cornerstone of administrative law, allocating responsibility for statutory construction between courts and agencies." (citation removed)).

53. *See West Virginia*, 597 U.S. at 723–25 (asserting that the major questions doctrine is a "label" that has been used to describe a body of law that has developed over the years in cases like *Brown & Williamson*, *MCI*, and *Utility Air*) (citing FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000); MCI Telecomms. Corp. v. Am. Tel. & Tel. Co., 512 U.S. 218 (1994); Util. Air Regul. Grp. v. EPA, 573 U.S. 302 (2014)); *cf. West Virginia*, 597 U.S at 766 (Kagan, J., dissenting) ("The majority today . . . announces the arrival of the 'major questions doctrine,' which replaces normal text-in-context statutory interpretation with some tougher-to-satisfy set of rules."). Since then the Court has applied the doctrine to invalidate President Biden's student debt forgiveness program. *See* Biden v. Nebraska, 600 U.S. 477, 500–07 (2023).

54. *See West Virginia*, 597 U.S. at 723–24.

requires of courts reviewing agency action cannot be squared with the APA."[55]

In theory, abortion could be considered a "major question" that Congress did not intend the FDA to decide when it empowered the agency to determine which drugs are safe and effective.[56] And *Dobbs* lends support to a distinct but related argument that, since states are now empowered to ban abortion, Congress must specify that the FDA can approve drugs that induce abortions. Moreover, in the wake of *Chevron*'s demise, courts might be more willing to substitute their interpretation of safety or effectiveness for the FDA's.

Early returns on such arguments, however, are not promising. While we can state with great confidence that the FDA's authority to regulate medication abortion will be subject to vigorous challenges, we predict (with some confidence) that the FDA should emerge (relatively) unscathed. With respect to both major questions and APA arbitrary and capricious challenges, federal courts appear reticent to substitute their judgment for the FDA's scientific expertise particularly in the realm of drug approval, where the FDA's congressionally delegated regulatory authority is fairly ironclad.

West Virginia's invocation of abortion as a "major question" met with a chilly reception in federal district court. The state claimed that because abortion is a "major policy decision . . . Congress did not intend to delegate the authority to the FDA to decide access issues for mifepristone."[57] The court emphatically rejected the state's claim that this was a situation involving "novel agency interpretations of long-standing ambiguous regulatory provisions as major grants of authority to reconfigure large aspects of the economy."[58] Rather, the court concluded that "the FDA is acting narrowly pursuant to an explicit grant of authority as to a single prescription medication."[59] Indeed, it opined that:

> [c]alling this a "major questions case" and demanding that the FDA refrain from treating abortion medications on par with other

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55. *See Loper Bright*, 144 S. Ct. at 2263. Moreover, as Justice Kagan remarked in dissent: "[I]t is impossible to pretend that today's decision is a one-off, in . . . its treatment of agencies . . . . [T]his very Term presents yet another example of the Court's resolve to roll back agency authority, despite congressional direction to the contrary." *Id.* at 2311 (Kagan, J., dissenting) (citing SEC v. Jarkesy, 144 S. Ct. 2117 (2024)).

56. *See, e.g.*, Daniel T. Deacon & Leah M. Litman, *The New Major Questions Doctrine*, 109 VA. L. REV. 1009, 1015–16 (2023) ("Now is an especially important time to unpack and assess the major questions doctrine. . . . [T]he federal government is reportedly considering and undertaking some administrative responses to secure access to abortion, particularly medication abortion.").

57. GenBioPro, Inc. v. Sorsaia, No. 3:23-0058, 2023 WL 5490179, at *3 (S.D.W. Va. Aug. 24, 2023).

58. *Id.* at *4.

59. *Id.*

> medications under the FDCA would make just as much sense as demanding the [Fish and Wildlife Service] refrain from listing the snail darter as an endangered species under the [Endangered Species Act].

And while the FDCA does not mention abortion, quipped the court, nor does it "mention any other specific procedure, device, cosmetic, or medication it instructs the FDA to regulate."[60]

Likewise, a federal district court in North Carolina concluded with little fanfare that the FDA has clear statutory authority to implement a Risk Evaluation Mitigation Strategy (REMS) for mifepristone.[61] It rejected a major questions challenge claiming that the FDA aggrandized its authority by "set[ting] national abortion policy" via the mifepristone REMS.[62] Rather, the court held that the FDCA straightforwardly authorizes the agency to implement REMS programs for all manner of drugs "without regard to their purpose; it does not impose different tests or rules for drugs that treat thyroid conditions or diabetes or any other conditions."[63]

Turning to the demise of *Chevron*, the FDA has a solid record of deference in the federal Courts of Appeals, including in cases not invoking *Chevron*.[64] Moreover, the FDA is especially well-positioned to withstand *Chevron*'s fall—particularly in the realm of new drug approvals—because the governing statutes are not ambiguous, and courts are comfortable deferring to the agency's scientific expertise.[65] Consider an example that surfaced during oral argument for *Loper Bright*'s companion case, *Relentless v. Department of Commerce*. Justice Jackson asked whether Congress intended the term "adequate and well-controlled investigation" to

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60. *Id.* (citing 21 U.S.C. § 321(h)(1) (defining "medical devices" without specifying any particular device)); *see also id.* at *5 ("The fact that Congress did not specify that mifepristone is to be used for abortion when it incorporated the drug into the REMS scheme is of no more import than its lack of specification as to isotretinoin's usage as an acne medication. . . . An order to regulate an express list of prescription medicines under a second list of articulated criteria is about as granular a grant of authority as Congress ever gives an agency.").

61. The REMS statute allows the FDA to impose restrictions on the conditions of use of an FDA-approved drug based on a risk-benefit analysis. *See* 21 U.S.C. § 355-1(f)(1)(3); *infra* notes 188–93 and accompanying text (discussing REMS in more detail).

62. Bryant v. Stein, No. 1:23-CV-77, 2024 WL 1886907, at *20 (M.D.N.C. Apr. 30, 2024).

63. *Id.*

64. *See supra* note 31; *see also* Liam Bendicksen, Aaron S. Kesselheim & C. Joseph Ross Daval, *FDA and* Chevron *Deference: A Case Review*, 78 FOOD & DRUG L.J. 371, 374, 386–90 (2023) (finding, over the course of 22 years (between 2000 and 2022), that in 26 cases in which federal appellate courts applied *Chevron* when the FDA claimed statutory authority, the statute was found unambiguous in 16, and the remaining 10 were decided in the FDA's favor).

65. *Cf.* Lisa Schultz Bressman, *Lower Courts After* Loper Bright, 31 GEO. MASON L. REV. 499 (2024) (arguing that courts will likely still defer to agency interpretations of more specialized terms after the overruling of *Chevron*).

be interpreted by the courts or by the FDA.[66] Justice Jackson was referring to the requirement that the FDA deny new drug applications that lack "substantial evidence" of effectiveness, further defined as evidence "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience."[67] There is likely no appetite among the courts to inject great uncertainty into the drug approval system by reinterpreting this provision, especially given that it includes an explicit reference to the judgment of "experts qualified by scientific training and experience."

By contrast, whether a "new product designed to promote healthy cholesterol levels [is] a dietary supplement or a drug"—a hypothetical raised by Justice Kagan during oral argument[68]—is a question courts might be more apt to ask, in part because it implicates the jurisdiction of the FDA. But that does not mean the end of *Chevron* will effect significant changes to deference to the FDA's drug approval decisions. As discussed above, dietary supplement and tobacco manufacturers have greater incentives to challenge the FDA's underlying statutory regulatory authority. Pharmaceuticals raise different questions, partly because the need for scientific expertise is embedded in the statute, and partly because industry groups are not incentivized to undermine the FDA's regulatory power.

Moreover, *Loper Bright* lends doctrinal support to these pragmatic reasons why the FDA's scientific expertise is likely to withstand post-*Chevron* challenges. Although courts can no longer defer to agency interpretations of ambiguous statutory provisions by default,[69] they *can* defer to agency authority when "the best reading of a statute is that it delegates discretionary authority to an agency."[70] It stands to reason that courts will be more willing to find such discretionary authority when they are less comfortable interpreting the meaning of a scientific or technical term.[71] The *Loper Bright* majority insisted that courts can (and often must) interpret "technical statutory questions,"[72] but at the same time it noted that courts "do not decide such questions blindly" and "will go about [their] task

66. Transcript of Oral Argument at 67, 72–73, Relentless, Inc. v. Dep't of Com., No. 22-1219 (U.S. Jan. 17, 2024).

67. 21 U.S.C. § 355(d). The agency has promulgated regulations defining "adequate and well-controlled investigations" in great detail. *See* 21 C.F.R. § 314.126 (2024).

68. Transcript of Oral Argument, *supra* note 66, at 11.

69. *See* Loper Bright Ents. v. Raimondo, 144 S. Ct. 2244, 2273 (2024).

70. *Id.* at 2263.

71. See *id.* at 2298 (Kagan, J., dissenting) ("[A]gencies often know things about a statute's subject matter that courts could not hope to. The point is especially stark when the statute is of a 'scientific or technical nature.'" (quoting Kisor v. Wilkie, 588 U.S. 558, 571 (2019))).

72. *Id.* at 2267 (majority opinion).

with [an] agency's 'body of experience and informed judgment,' among other information, at [their] disposal."[73]

To be sure, the Court has substituted *Skidmore* "power to persuade" deference (or "respect") for *Chevron* mandatory deference, but—at least as concerns the FDA—we do not expect seismic shifts in outcomes.[74] For, as the Court repeatedly insists:

> In exercising such judgment . . . courts may—as they have done from the start—seek aid from the interpretations of those responsible for implementing particular statutes. Such interpretations "constitute a body of experience and informed judgment to which courts and litigants may properly resort for guidance" consistent with the APA.[75]

Moreover, that body of experience should be most persuasive when the interpretive question before a court is a highly technical question that Congress intended (based on some evidence, itself subject to interpretation) to delegate to the agency's expertise.[76] Though courts are not *required* to defer to an agency's decision that, for example, an alpha amino acid polymer is a "protein,"[77] they are *likely* to do so in the context of the FDA's express mandate to decide which drugs are safe and effective.[78]

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73. *Id.* (quoting Skidmore v. Swift & Co., 323 U.S. 134, 140 (1944)); *see also id.* at 2259 ("The 'interpretations and opinions' of the relevant agency, 'made in pursuance of official duty' and 'based upon . . . specialized experience,' 'constitute[d] a body of experience and informed judgment to which courts and litigants [could] properly resort for guidance' even on legal questions." (quoting *Skidmore*, 323 U.S. at 139–40)).

74. Under *Skidmore*:

> "The weight of such a judgment in a particular case," the Court observed, would "depend upon the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade, if lacking power to control."

Id. at 2259 (quoting *Skidmore*, 323 U.S. at 140).

75. *Id.* at 2262 (quoting *Skidmore*, 323 U.S. at 140).

76. In terms of reliance on agency expertise, the Court stated that, while not technically binding on a court, an agency's interpretation "may be especially informative 'to the extent it rests on factual premises within [the agency's] expertise.'" *Id.* at 2267 (quoting Bureau of Alcohol, Tobacco, and Firearms v. FLRA, 464 U.S. 89, 98 n.8 (1983)). "Such expertise has always been one of the factors which may give an Executive Branch interpretation particular 'power to persuade, if lacking power to control.'" *Id.* at 2267 (quoting *Skidmore*, 323 U.S. at 140).

77. *See id.* at 2298 (Kagan, J., dissenting); *see also supra* note 27.

78. Thus, while the dissent raises the fear that the majority's decision "gives courts the power to make all manner of scientific and technical judgments," *id.* at 2311, we have more confidence that courts will eschew doing so, both for pragmatic reasons, but also consistent with *Loper Bright*'s doctrinal framework centered on implied delegation of authority and *Skidmore* "power to persuade" deference.

2. "Arbitrary and Capricious" Challenges

In April 2023, a federal district court in Texas shocked the nation by invalidating the FDA's approval of mifepristone (two decades earlier), as well as the agency's subsequent actions to impose (and then remove) certain restrictions on the medication abortion pill.[79]

The court concluded that the FDA had impermissibly misinterpreted the Subpart H statutory provision, and that its actions on mifepristone were arbitrary and capricious.[80] The court recounted how Subpart H[81] allowed for accelerated approval by applying certain restrictions to drugs that (1) have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and (2) provide a meaningful therapeutic benefit to patients over existing treatments.[82] Glibly citing "Sesame Street," the court asserted that pregnancy is unambiguously not an "illness,"[83] and therefore it refused to defer to the FDA's interpretation of the term.[84] Likewise, the court refused to credit the FDA's determination that mifepristone provides a meaningful therapeutic benefit.[85]

The court further concluded that the FDA's approval of and subsequent actions on mifepristone were arbitrary and capricious because the agency failed to consider a litany of important aspects,[86] such as the psychological and long-term effects of the drug[87] and the need to require transvaginal ultrasounds to diagnose ectopic pregnancies.[88] The court claimed it "does

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79. All. for Hippocratic Med. v. FDA, 668 F. Supp. 3d 507, 560 (N.D. Tex. 2023). For a discussion of the agency's other post-approval actions on mifepristone, see *supra* note 1 and accompanying text.

80. *See id.* at 554 ("There is also evidence indicating FDA faced significant political pressure to forego its proposed safety precautions to better advance the *political* objective of increased 'access' to chemical abortion . . . .").

81. Whether the FDA in fact approved mifepristone under the Subpart H provision is disputed:

> Although the lower courts characterize the approval of mifepristone as an "accelerated approval," FDA uses that term to refer to a separate provision of Subpart H (21 C.F.R. § 314.510), which provides for the accelerated approval of a drug product based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. FDA did not invoke that provision in connection with the approval of mifepristone.

Brief for Food and Drug Law Scholars as *Amici Curiae* in Support of Applicants at 6, FDA v. All. for Hippocratic Med., Nos. 22A902 & 22A901 (U.S. Apr. 14, 2023).

82. *See All. for Hippocratic Med.*, 668 F. Supp. 3d at 543–44 (citing 21 C.F.R. §§ 314.500, 314.560 (2024)).

83. *Id.* at 545.

84. *See id.* at 545–46 (refusing to grant *Auer* deference because the language of the regulation is plain and unambiguous (citing Kisor v. Wilkie, 588 U.S. 558, 563–79 (2019))).

85. *See id.* at 546–48; *see also id.* at 548 ("Simply put, FDA's data are incomplete and potentially misleading, as are the statistics touted by the mifepristone advocates.").

86. *See id.* at 549–57.

87. *Id.* at 550–52.

88. *Id.* at 551–53.

not second-guess FDA's decision-making lightly. But here, FDA acquiesced on its legitimate safety concerns—in violation of its statutory duty—based on plainly unsound reasoning and studies that did not support its conclusions."[89] For similar reasons, the court likewise found the FDA's 2016 and 2019 actions on mifepristone arbitrary and capricious.[90]

This assault on the FDA's scientific judgment alarmed the Biden Administration, which quickly sought and received a stay from the U.S. Supreme Court pending disposition of an appeal in the Fifth Circuit and a writ of certiorari.[91] During oral argument before the Fifth Circuit, the government's characterization of the district court's order as "an unprecedented and unjustified attack on FDA's scientific expertise" and insistence that "it's not a court's role to come in and second-guess that expertise, and no court has ever done that,"[92] provoked a response from Judge Ho that foreshadowed where the court was headed: "I don't understand this theme that FDA can do no wrong. We are allowed to look at the FDA just like we're allowed to look at any agency. That's the role of the courts."[93]

The Fifth Circuit vacated the district court's invalidation of the FDA's 2000 mifepristone approval on timeliness grounds.[94] However, the Fifth Circuit agreed that the agency's 2016 amendments to the mifepristone REMS and the 2021 decision not to enforce the in-person prescription requirement were arbitrary and capricious.[95] In the court's view, the FDA failed to consider the "cumulative effect" of the 2016 amendments. Though the FDA had studied the changes—including increasing the maximum gestational age from 7 to 10 weeks and allowing non-physicians to prescribe mifepristone—individually, in the Fifth Circuit's eyes, the agency erred by failing to consider the effect of implementing all of the changes together.[96] According to the court, the FDA also failed to consider whether it needed to continue to collect data from non-fatal adverse events in light of the

89. *Id.* at 554.
90. *See id.* at 555–56.
91. *See* Danco Laby's, LLC v. All. For Hippocratic Med., 143 S. Ct. 1075 (2023).
92. *See* Abbie VanSickle & Pam Belluck, *Appeals Court Seems Skeptical of F.D.A.'s Approval and Regulation of Abortion Pill*, N.Y. TIMES (May 17, 2023), https://www.nytimes.com/2023/05/17/us/politics/abortion-pill-case-arguments.html [https://perma.cc/X5FE-PUCY] (quoting the U.S. Deputy Assistant Attorney General for Civil Appellate, representing the FDA).
93. *See* Debra Cassens Weiss, *'I Don't Understand this Theme That FDA Can Do No Wrong,' Says 5th Circuit Judge on Mifepristone Approval*, ABA JOURNAL (May 18, 2023), https://www.abajournal.com/news/article/5th-circuit-judge-on-mifepristone-approval-i-dont-understand-this-theme-that-fda-can-do-no-wrong [https://perma.cc/KHV3-MNK4].
94. All. for Hippocratic Med. v. FDA, 78 F.4th 210, 245 (5th Cir. 2023).
95. *See id.* at 245–49.
96. *Id.* at 245–46.

amendments.[97] Furthermore, the court found that the 2021 non-enforcement decision erroneously relied on insufficient data and scientific studies that contradicted its conclusion.[98]

The historical trend of longstanding deference to the FDA's scientific expertise when directly challenged puts the scientific second-guessing that the Fifth Circuit and the district court did in *Alliance for Hippocratic Medicine* in sharp relief. In its *Alliance* certiorari petition, the FDA framed the decisions below as "the first time any court has restricted access to an FDA-approved drug based on disagreement with FDA's expert judgment about the conditions required to assure that drug's safe use."[99] When asked during oral argument whether the agency stood by this statement, the Solicitor General answered: "we, on behalf of FDA, think that courts have no business making those judgments in the absence of the kind of arbitrary and capricious error that would satisfy the APA."[100] Both in its brief and during oral argument, the FDA repeatedly cited the scientific evidence it had reviewed in support of its various actions on mifepristone.[101] The agency maintained that the "deferential arbitrary and capricious standard does not give litigants or the courts a license to 'unduly second-guess' the agency's 'scientific judgments.'"[102]

The U.S. Supreme Court, which dismissed the case for lack of standing,[103] will likely have the last word on the level of deference (or, in *Loper Bright*'s reformulation, "respect") due to the FDA's scientific expertise if and when the question returns to the Court.[104] Against the

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97. *Id.* at 246–47.

98. *Id.* at 249–51.

99. Petition for Writ of Certiorari at 11–12, FDA v. All. for Hippocratic Med., 602 U.S. 367 (2024) (No. 23-235).

100. Transcript of Oral Argument at 36, FDA v. All. for Hippocratic Med., 602 U.S. 367 (2024) (No. 23-235).

101. *See* Petition for Writ of Certiorari, *supra* note 99, at 4–7, 21–27.

102. *Id.* at 26–27 (quoting Pharm. Mfg. Rsch. Servs., Inc. v. FDA, 957 F.3d 254, 262 (D.C. Cir. 2020) (quoting Cytori Therapeutics, Inc. v. FDA, 715 F.3d 922, 923 (D.C. Cir. 2013) (Kavanaugh, J.))).

103. *All. for Hippocratic Med.*, 602 U.S. at 396.

104. The key unanswered question, as Justice Jackson asked the attorney for Alliance at oral argument, is: "[W]hat deference, if any, do courts owe the opinion of the expert agency concerning the safety and efficacy of drugs?" Transcript of Oral Argument, *supra* note 100, at 97.

In the wake of *Alliance*, anti-abortion groups are circling the wagons. *See* Kelcie Moseley-Morris & Sofia Resnick, *Anti-Abortion Groups Say Supreme Court's Mifepristone Ruling Won't Deter Them*, IDAHO CAP. SUN (June 14, 2024, 11:54 AM), https://idahocapitalsun.com/2024/06/14/anti-abortion-groups-say-supreme-courts-mifepristone-ruling-wont-deter-them [https://perma.cc/BEG6-YP2J] (surveying various anti-abortion group leaders and legal advocates). Anticipating the Court's dismissal of the suit, a coalition of red states—whose motion to intervene in *Alliance* was denied by the Supreme Court—had been planning to launch a future suit. *See* Ian Lopez, *Supreme Court Denies Red States' Bid in Abortion Pill Row*, BLOOMBERG L. NEWS (Feb. 20, 2024, 4:58 PM), https://www.bloomberglaw.com/bloomberglawnews/health-law-and-business/X2F1V830000000?bna_news_filter=health-law-and

backdrop of the robust record of judicial deference to the FDA's scientific expertise in direct challenges to its actions, particularly on drugs (see *supra* Section I.A), we predict that, ultimately, deference to the FDA's scientific judgment will carry the day.[105]

II. INDIRECT CHALLENGES

FDA actions can be challenged directly on administrative and constitutional grounds (as detailed in Part I). Equally potent, but typically not conceived of as such, are what amount to *indirect* challenges to FDA actions.[106]

Indirect challenges come in two forms. The first type occurs by way of a federal preemption defense to a state-law tort claim. The second type is a state positive law that contradicts FDA actions. These are indirect, rather than direct, challenges to FDA actions because they assert state authority while assuming *sub silentio* that any FDA regulation to the contrary is invalid or inapplicable.

Historically, states have only occasionally asserted their police powers to enact health and safety laws that contradict FDA determinations. Such indirect challenges have proliferated post-*Dobbs*. State laws banning abortion generally or abortion pills in particular do not directly challenge the FDA's decision to approve the abortion pill mifepristone. Rather, they represent the assertion of states' police powers as an indirect challenge to federal law.

It is not only novel but also instructive to consider these distinct lines of jurisprudence under the common banner of indirect challenges to FDA

-business#jcite [https://perma.cc/5BS2-YZ3J] (noting that the states will have "the opportunity to pursue separate legal action" should the Court dismiss *Alliance* on standing grounds).

105. The Justices did not show their hands on this issue during oral argument given the almost singular focus on the issue of standing, save a few hints that foreshadow (not surprisingly) some division of opinion. At one end of the spectrum, Justice Alito—channeling Fifth Circuit Judge Ho—asked the attorney representing Danco Labs: "Do you think the FDA is infallible?" Transcript of Oral Argument, *supra* note 100, at 52. At the other end, Justice Jackson chimed in: "So you were asked if the agency is infallible . . . I'm wondering about the flip side which is do you think that courts have specialized scientific knowledge with respect to pharmaceuticals? . . . [D]o you have concerns about judges parsing medical and scientific studies?" *Id.* at 58. Moreover, the Court's division in *Loper Bright* (with Justice Alito in the majority and Justice Jackson in dissent) adds some degree of uncertainty.

106. *See* Catherine M. Sharkey, State Farm *"With Teeth": Heightened Judicial Review in the Absence of Executive Oversight*, 89 N.Y.U. L. REV. 1589, 1635 (2014) ("[C]ourts entertain what are in effect *indirect challenges* to agency preemptive rulemakings and interpretive positions: Parties raise preemption defenses to civil claims in contexts where there is an underlying federal regulator, such as in banking and numerous areas of products liability (e.g., automobiles, recreational boats, pharmaceuticals, medical devices)." (emphasis added)); Sharkey, *Federalism Accountability*, *supra* note 13, at 2184–85 ("*Wyeth v. Levine* . . . stands as a progenitor of a new form of *indirect challenge*, arising when the preemption defense is raised against state tort causes of action." (emphasis added)).

action. By doing so, it becomes clear that challenges to state positive laws that involve areas of concurrent state and federal authority call upon courts to engage in an analysis that closely resembles the analysis used in implied preemption cases.

A. Federal (Not State) Approval of Drugs and Medical Devices

Congress created the FDA to replace a scheme of state-by-state regulation of drugs, which was "seriously deficient, since a state could not enforce its regulations against an out-of-state manufacturer."[107] In response to public outrage generated by the "exposure of tonics as cheap cocktails in disguise and of soothing syrups as opiates for infants," Congress enacted the Pure Food and Drugs Act of 1906.[108] The Agriculture Department's Bureau of Chemistry was responsible for determining whether food and drugs were misbranded or adulterated.[109]

In 1938, Congress empowered the FDA to evaluate the safety of drugs, setting up a single, national premarket review system under the Food Drug and Cosmetic Act (FDCA). Congress was reacting to the Elixir Sulfanilamide disaster.[110] That drug, manufactured in Tennessee, killed "[a]t least 73, perhaps over 90, persons in various parts of the country, although chiefly in the South."[111] The FDA conducted a national search for 240 gallons of the Elixir, which had been distributed across the country.[112] This national problem demanded a national solution. Accordingly, Senator Royal S. Copeland (a homeopathic physician by trade) proposed a provision—part of which was ultimately enacted—that forbade the interstate marketing of drugs "not generally recognized as safe for use" unless the FDA found that the drug was safe.[113]

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107. Oscar E. Anderson, Jr., *Pioneer Statute: The Pure Food and Drugs Act of 1906*, 13 J. PUB. L. 189, 190 (1964).

108. *See id.* at 193.

109. Enforcement lay in the hands of either the Bureau or the Secretary to decide whether to refer matters to what we now call DOJ for court enforcement (seizure or criminal). *See id.* at 194–95 ("It could be argued that the [Agriculture Department's] Bureau of Chemistry was to act as a grand jury to submit evidence of violations to the Secretary for transmittal to district attorneys for prosecution. . . . On the other hand, it could be maintained that the pure-food law authorized the Secretary to decide what matters should be carried to the courts.").

110. Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1761 (1996) (citing David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 L. & CONTEMP. PROBS. 2, 20 (1939)).

111. Cavers, *supra* note 110, at 20.

112. *Id.*

113. *See id.*; *see also* James Egge, *Dr. Copeland and the 1918-19 Pandemic*, E. MAG. (2021), https://magazine.emich.edu/spring-2021/dr-copeland-and-the-1918-19-pandemic [https://perma.cc/P7DD-LRBY] ("While in the Senate [Copeland] became one of the country's most popular physicians,

With its 1962 Amendments to the FDCA, Congress "converted what had been a [national] premarket *notification* system . . . into a [national] premarket *approval* system, in which the [drug] maker was obliged to wait for agency officials to affirm the drug's safety *and* effectiveness."[114] The 1962 Amendments strengthened the FDA's premarket regulatory powers in three ways: by granting the agency effective veto power over the marketing of any new drug; by raising the standards by which drugs were evaluated to confirm their safety *and* effectiveness; and by empowering the FDA to set the standards for the clinical trials necessary to demonstrate a drug's safety and effectiveness.[115] Crucially, the provisions related to drugs did not expressly preempt inconsistent state laws.

In 1976, in response to a "series of high-profile medical device failures that caused extensive injuries and loss of life,"[116] Congress added medical devices to the nationalized premarket approval system for drugs under the FDCA.[117] Congress also included the Medical Devices Amendments (MDA), which expressly preempts state laws that deviate from FDA determinations about device safety and effectiveness. States cannot:

> establish or continue in effect with respect to a device intended for human use any requirement
>
> (1) which is different from, or in addition to, any requirement applicable under [federal law] to the device, and
>
> (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under [relevant federal law].[118]

Just as Congress replaced state-by-state drug regulation with a federal scheme, the MDA's national preclearance scheme supplanted state-by-state

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dispensing health advice in a daily newspaper column, a radio show, and a book, 'Dr. Copeland's Home Medical Book.'").

114. Merrill, *supra* note 110, at 1764–65.

115. *See id.* at 1764–67.

116. Riegel v. Medtronic, Inc., 552 U.S. 312, 336 (2008) (Ginsburg, J., dissenting) (citing H.R. REP. NO. 94-853, at 8 (1976); S. REP. NO. 94-33, at 6 (1975)).

117. *See* S. REP. NO. 94-33, at 6–7 (1975) (discussing the formation, findings, and recommendations of the Cooper committee, which recommended legislation to create a federal preclearance scheme for medical devices akin to that for drugs). The Senate Report chronicles the difficulties of combatting the sale and marketing of "quack" and "fraudulent" devices before the MDA, which was a result of the FDA's inability to assess the safety and efficacy of devices *before* they went to market. *See id.* at 2–3.

118. 21 U.S.C. § 360k(a).

medical device regulations.[119] According to the House Report, Congress feared that "if a substantial number of differing requirements applicable to a medical device are imposed by jurisdictions other than the Federal government," it would unduly burden interstate commerce.[120] It noted that "[i]n the *absence* of effective Federal regulation of medical devices," states were developing their own regulations.[121]

Clearly Congress wanted to—and did—create a *federal* preclearance scheme. Yet Congress contemplated that complementary state positive laws regarding medical devices could coexist with the federal scheme in "some situations in which regulation of devices by States and localities would constitute a *useful supplement* to Federal regulation."[122] The FDA can grant preemption exemptions for state requirements in their final form with the force and effect of law,[123] which are either more stringent than FDA regulations or required by compelling local conditions.[124] States can challenge the FDA's determination, though this appears to be exceedingly rare.[125]

The FDCA does not explicitly contemplate a complementary scheme of state *pharmaceutical* regulations.[126] Indeed, the U.S. Supreme Court has balked at efforts to interpret the FDCA to allow the interstate use of non-FDA approved drugs. In *United States v. Rutherford*, terminally ill cancer patients sued the FDA, which had not approved a cancer treatment called

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119. *See Riegel*, 552 U.S. at 333 (Ginsburg, J., dissenting) ("Until 1976, the Federal Government did not engage in premarket regulation of medical devices. Some States acted to fill the void by adopting their own regulatory systems for medical devices. Section 360k(a) responded to that state regulation, and particularly to California's system of premarket approval for medical devices, by preempting State initiatives absent FDA permission.").

120. H.R. REP. NO. 94-853, at 45 (1976).

121. *Id.* (emphasis added). The most comprehensive state scheme was California's Sherman Law, which "resulted in the requirement that intrauterine devices are subject to *premarket clearance in California*." *Id.* (emphasis added).

122. *Id.* (emphasis added). Congress cited the Sherman Law as an "example of requirements that the Secretary should authorize to be continued (provided any application submitted by a State meets requirements pursuant to the [MDA])." *Id.* at 46. Today, the Sherman Law has been amended to account for the preemptive federal preclearance scheme. *See* CAL. HEALTH & SAFETY CODE § 111245 (West 2024).

123. *See* 21 U.S.C. § 360(k)(b); 21 C.F.R. § 808.20(a) (2024).

124. *See* 21 U.S.C. § 360k(b); 21 C.F.R. § 808.20(c)(4) (2024).

125. In the only prominent challenge to such a determination by the FDA, the First Circuit sided with the FDA. *See* Massachusetts v. Hayes, 691 F.2d 57 (1st Cir. 1982) (upholding FDA's denial of Massachusetts's exemption application for a broadly-applicable requirement of professional audiological testing by a physician or audiologist—rather than by hearing aid dealers—for hearing aid purchasers).

126. *See* Riegel v. Medtronic, Inc., 552 U.S. 312, 342 (2008) (Ginsburg, J., dissenting) ("[S]tate premarket regulation of medical devices, not any design to suppress tort suits, accounts for Congress' inclusion of a preemption clause in the MDA; *no such clause figures in earlier federal laws regulating drugs and additives, for States had not installed comparable control regimes in those areas*." (emphasis added)).

Laetrile.[127] The Court rejected the lower courts' determinations that the "safety and effectiveness" requirements did not apply to drugs used by terminally ill patients.[128] It found no textual or historical exemption for drugs used by the terminally ill.[129] Moreover, the Court feared that reading such an exemption into the statute would be tantamount to "deny[ing] the [FDA] Commissioner's authority over all drugs, however toxic or ineffectual, for [terminally ill] individuals."[130] The Court concluded that Congress intended to empower the FDA to protect *all* patients from "the vast range of self-styled panaceas that inventive minds can devise."[131] Indeed, Congress required that drugs be proven to be not just safe but *effective*, because "if an individual suffering from a potentially fatal disease rejects conventional therapy in favor of a drug with no demonstrable curative properties, the consequences can be irreversible."[132] The Court did not expressly say that states cannot legalize drugs the FDA had not approved. But it did note that, at the time, seventeen states had legalized the prescription and use of Laetrile for intrastate cancer treatment, though only after the litigation had commenced.[133] And the use of Laetrile dwindled after *Rutherford*, likely due to a combination of deference to the FDA's decision and the legal difficulties of disentangling intrastate from interstate distribution of Laetrile in a national market.[134]

B. The Preemption Defense

Despite scholarly criticism and the Supreme Court's waning faith in, and ultimate abandonment of, *Chevron*, *Skidmore*-type deference to the FDA remains strong when FDA actions are indirectly challenged through the defense of implied preemption to products liability actions.[135] In making

127. *See* United States v. Rutherford, 442 U.S. 544 (1979).
128. *See id.* at 550–51.
129. *See id.* at 552–54.
130. *Id.* at 557–58.
131. *Id.* at 558.
132. *Id.* at 556.
133. *Id.* at 554 n.10.
134. *See Laetrile/Amygdalin (PDQ®)–Health Professional Version*, NAT'L CANCER INST. (June 14, 2022), https://www.cancer.gov/about-cancer/treatment/cam/hp/laetrile-pdq [https://perma.cc/RNR4-T7KP] ("[L]aetrile was legalized in more than 20 states during the 1970s. In 1980, the U.S. Supreme Court acted to uphold a federal ban on interstate shipment of laetrile. As a result, the use of laetrile has greatly diminished, but the compound continues to be manufactured and administered as an anticancer therapy, primarily in Mexico, and in some clinics in the United States.").
135. *See* Sharkey, *Products Liability Preemption*, *supra* note 13, at 491–99 (arguing that courts give *Skidmore*, rather than *Chevron*, deference to administrative agency determinations of preemption); Catherine M. Sharkey, *The Administrative State and the Common Law: Regulatory Substitutes or Complements?*, 65 EMORY L.J. 1705, 1723–24 (2016) [hereinafter *The Administrative State and the*

preemption determinations, courts in essence recognize a complementary system of state common law and federal regulation of medical devices and pharmaceuticals.[136] When determining whether a state-law tort claim is preempted by FDA regulation, as part of its overall interpretive analysis, courts examine the agency's regulatory record and largely defer to it. Courts give "great weight" to input from the FDA based upon its regulatory cost-benefit determinations in this "agency reference" preemption framework. The agency reference framework, in other words, is a mode of judicial decision-making that gives deference to evidence-backed agency determinations.[137]

Courts' adjudication of failure-to-warn claims against brand-name drug manufacturers embodies this framework.[138] If there is "clear evidence that the FDA would not have approved a change" to a drug's label, then a plaintiff's failure-to-warn claim is preempted.[139] To establish clear evidence, a manufacturer must show that it "[1] fully informed the FDA of the justifications for the warning required by state law and [2] that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning."[140] To determine whether the first prong is satisfied, courts comb through the record to see what

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Common Law] ("Conservative core Justices—whose ire is stoked by any agency encroachment on judicial authority—are notably unfazed by agency encroachment on the common law of torts. Preemption cases in the arenas of pharmaceuticals and medical devices are particularly illustrative of this phenomenon."); *see also id.* at 1726 ("[T]he conservative core Justices' attack on *Auer* and *Chevron* deference, and wider distaste for and distrust of the administrative state, is suspended in federal preemption cases, given the doctrines of agency deference that are implicated.").

136. *See* Wyeth v. Levine, 555 U.S. 555, 578 (2009) ("In keeping with Congress' decision not to pre-empt common-law tort suits, it appears that the FDA traditionally regarded state law as a complementary form of drug regulation."); Patricia J. Zettler & Ameet Sarpatwari, *State Restrictions on Mifepristone Access — The Case for Federal Preemption*, 386 NEW ENG. J. MED. 705, 707 (2022) ("[S]tate litigation can address issues that the FDA typically doesn't consider, such as the quantity of drugs dispensed throughout a class (an issue raised in opioid litigation). State litigation can also serve purposes that are different from the goals of FDA oversight, including compensation of injured patients.").

137. *See supra* note 13.

138. State-law tort claims against *generic* drug manufacturers are preempted as a matter of impossibility preemption due to federal "sameness" directives requiring generic drug labels and warnings to match those of brand-name equivalents. *See* PLIVA, Inc. v. Mensing, 564 U.S. 604, 624–25 (2011).

139. *See Wyeth*, 555 U.S. at 571. Failure-to-warn claims are preempted unless the drug manufacturer could have provisionally changed its warning label without prior FDA approval under the "changes being effected" (CBE) provision. 21 C.F.R. § 314.70(c)(6)(iii)(A) (2024); *see* Gibbons v. Bristol-Meyers Squibb Co., 919 F.3d 699, 708 (2d Cir. 2019); Dolin v. GlaxoSmithKline LLC, 901 F.3d 803, 812 (7th Cir. 2018); *In re* Celexa & Lexapro Mktg. & Sales Pracs. Litig., 779 F.3d 34, 41 (1st Cir. 2015). If a state-law claim against a manufacturer addresses newly acquired information and addresses a design or labeling change that a manufacturer may unilaterally make without FDA approval, then there may be no preemption of that claim. *See Wyeth*, 555 U.S. at 569–70.

140. Merck Sharp & Dohme Corp. v. Albrecht, 587 U.S. 299, 303 (2019).

manufacturers sent to the FDA, including email correspondence, safety studies, and other submissions.[141] Courts occasionally solicit and regularly rely on the agency's input.[142] Likewise, to determine whether the second prong is satisfied, courts comb through submissions of alternative warnings submitted to the FDA and the FDA's responses.[143] Again, courts tend to defer to the agency's interpretation of its responses.[144] We expect the current Supreme Court's governing majority will continue to accord *Skidmore* deference to the FDA's decisions about drug safety, particularly in the context of failure-to-warn claims.[145]

State-law tort claims regarding medical devices can be expressly[146] or impliedly preempted. In these cases, courts also follow an agency reference model. Briefly stated, the Supreme Court has distinguished medical devices that have gone through the stringent premarket approval (PMA) review process—after which manufacturers cannot make changes that would affect safety or effectiveness without FDA approval—from devices that have gone through the less-stringent premarket notification (PMN), or Section 510(k), review process.[147] State-law tort design defect and failure-to-warn claims arising from PMA devices are preempted, while those arising from PMN devices are not. Recall that Section 360k(a) prohibits states from imposing "requirement[s]" that are "different from, or in addition to" FDA-imposed requirements.[148] The Court has held that because the PMA regulatory review for safety and efficacy imposes "requirement[s]" within the ambit of

141. *See, e.g.*, *In re* Fosamax (Alendronate Sodium) Prods. Liab. Litig., 593 F. Supp. 3d 96, 120–24 (D.N.J. 2022).

142. *See, e.g.*, *id.* at 125 ("If any doubt remains as to whether Defendant fully informed the FDA of the justification for its warning, the Agency itself agrees that Defendant 'provided [it] with the relevant scientific data about Fosamax's risks.'" (citing Brief for the United States as Amicus Curiae Supporting Petitioner, *Albrecht*, 587 U.S. 299 (No. 17-290))).

143. *See, e.g.*, *id.* at 125–45.

144. *See, e.g.*, *id.* at 135 (deferring to the FDA's interpretation of its response to the defendant's proposed warning, as articulated in the agency's amicus brief, because "an agency's fair and considered judgment as to the meaning of its own regulation and actions deserves some measure of deference").

145. *Albrecht* indicates that, save for Justice Thomas, there is a broad consensus in favor of the agency reference model for implied preemption on the current Court. Justice Alito, joined by Chief Justice Roberts and Justice Kavanaugh, concurred in the judgment but wrote separately to highlight the impact of 21 U.S.C. § 355(o)(4)(A) on preemption analysis. *See Albrecht*, 587 U.S. at 323 (Alito, J., concurring). This provision requires the FDA to initiate a label change if it becomes aware of new information that should be included on the label. *See id.* at 324. Justice Thomas joined the majority opinion but authored a concurrence to critique the implied preemption framework. *See id.* at 318 (Thomas, J., concurring).

146. *See* 21 U.S.C. § 360k(a) (providing that a state cannot "establish or continue in effect with respect to a device intended for human use any requirement— (1) which is different from, or in addition to, any requirement applicable under [federal law] to the device, and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under" relevant federal law).

147. *See* Riegel v. Medtronic, Inc., 552 U.S. 312, 317–19 (2008).

148. 21 U.S.C. § 360k(a).

Section 360k(a), state-law tort claims seeking to impose different or additional requirements are preempted.[149] By contrast, devices that enter the market through the PMN, or Section 510(k), process are merely tested for substantial equivalence to a product that is already on the market (i.e., not for safety and efficacy). Therefore, the Court has held that state-law tort claims regarding such devices are *not* preempted because the FDA does not require them to "take any particular form for any particular reason."[150] Indeed, many lower courts, following the FDA's guidance, have analyzed PMA- and PMN-approved components in the same device separately for preemption purposes.[151]

There are some gaps in implied preemption doctrine. For example, whether federal law preempts state-law tort claims based on off-label promotion is an unsettled issue.[152] As a matter of express preemption, in 2023, Congress amended the FDCA to authorize the FDA to ban particular uses of medical devices.[153] But the FDCA does not otherwise directly address whether medical providers can prescribe or administer a device or drug for an off-label use. It only regulates manufacturers' ability to promote off-label uses by essentially prohibiting marketing and advertising of such off-label uses.[154] How courts approach the issue could determine whether

149. *Riegel*, 552 U.S. at 322–23, 330.

150. *Id.* at 323 (quoting Medtronic, Inc. v. Lohr, 518 U.S. 470, 493 (1996)).

151. *See* Shuker v. Smith & Nephew, PLC, 885 F.3d 760, 772–74 (3d Cir. 2018) (soliciting the FDA's input and relying on the agency's amicus brief to conclude that preemption analysis for hybrid devices must be done component-by-component); *In re* Smith & Nephew Birmingham Hip Resurfacing (BHR) Hip Implant Prods. Liab. Litig., 401 F. Supp. 3d 538, 551–52 (D. Md. 2019) (concluding based on *Shuker* and the FDA's amicus brief therein that "§ 360k(a) does not extend to state law claims that target the § 510(k)-approved components or the system as a whole"); White v. Medtronic, Inc., 808 F. App'x 290, 294–95 (6th Cir. 2020) (agreeing with the *Shuker* court that claims related to component parts of a PMA device can be preempted when used separately). *But see* Simon v. Smith & Nephew, Inc., 18 F. Supp. 3d 423, 429 (S.D.N.Y. 2014) ("[The preemption] inquiry focuse[s] on the device as a whole, rather than its individual components.").

152. *See* David A. Simon, *Off-Label Preemption*, 2024 WISC. L. REV. 1079, 1124 ("Under [the author's review theory], the doctrine of preemption applies only when the risks involved have been reviewed by FDA *as to approved uses*. When FDA has not yet reviewed a risk or has reviewed a risk associated with a use it has not approved, preemption should not apply. Since most off-label risks may not be reviewed by FDA nor expected to be part of risk-benefit calculus as to the *approved use*, federal law should not preempt state law claims based on off-label promotion." (second emphasis added)).

153. *See* Consolidated Appropriations Act of 2023, Pub. L. No. 117-328, 136 Stat. 4459, 5834 (amending the FDCA to authorize the FDA to ban "one or more intended uses" of a medical device—rather than just the entire device—if the device presents "an unreasonable and substantial risk of illness or injury for one or more intended uses") (codified at 21 U.S.C. § 360f(a)(1)).

154. The FDCA prohibits "[t]he introduction or delivery for introduction into interstate commerce of any . . . drug, [or] device . . . that is . . . misbranded." 21 U.S.C. § 331(a). A drug is misbranded if its labeling does not bear "adequate directions for use." 21 U.S.C. § 352(f). FDA regulations define these as "directions under which the layman can use a drug safely *and for the purposes for which it is intended*." 21 C.F.R. §201.5 (2024) (emphasis added). Drug manufacturers and their representatives retain First Amendment protections that allow them to promote off-label use in ways that are not false or misleading. *See* United States v. Caronia, 703 F.3d 149, 164–66 (2d Cir. 2012).

states can ban off-label uses of drugs such as mifepristone and puberty blockers—issues we take up in Part IV, *infra*.

C. State Bans of FDA-Approved Drugs

Although the current proliferation of state laws banning FDA-approved drugs is not without historical analog, courts are bereft of a coherent doctrinal framework within which to analyze these potential state-federal law clashes. In the realm of products liability claims involving FDA-approved pharmaceuticals and medical devices, the U.S. Supreme Court has molded preemption doctrine to serve the complementary aims of state tort law and federal law. No such judge-made doctrine exists to help courts navigate conflicts between state positive law and FDA regulations.

Precisely how courts should police the boundary between impermissible state regulations of drug safety and permissible state regulations of health and safety or the practice of medicine is unclear. It is undisputed that an agency regulation with the force of law can preempt conflicting state requirements.[155] At the same time, historically there was a presumption that "state or local regulation[s] of matters related to health and safety [are] not invalidated under the Supremacy Clause."[156] Public health crises have prompted Congress to expand the federal government's regulatory authority into these historically state law areas. Such crises have simultaneously prompted states to flex their regulatory muscles into the federal regulatory domain, in ways that have contradicted, complemented, and supplemented FDA actions.

What should a court do when a state attempts to ban an FDA-approved drug? The safety and effectiveness of drugs is squarely within the FDA's purview.[157] But the states retain their police powers over health and safety and the practice of medicine. Pre-*Dobbs*, a handful of lower courts faced such state-federal law clashes; *Dobbs* raises the stakes quantitatively (in terms of numbers of such clashes) and qualitatively (in terms of policy significance).

In 2014, Massachusetts Governor Deval Patrick declared a public health emergency related to the FDA-approved, highly potent opioid analgesic Zohydro ER. Consequently, the state's public health commissioner banned the drug by prohibiting the prescription, ordering, dispensing, and

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155. *See* Wyeth v. Levine, 555 U.S. 555, 576 (2009) (citing Geier v. Am. Honda Motor Co., 529 U.S. 861 (2000); Hillsborough Cnty. v. Automated Med. Lab'ys, Inc., 471 U.S. 707, 713 (1985)).

156. *Hillsborough Cnty.*, 471 U.S. at 715–16 (finding that local ordinances regulating plasma donation were not preempted by the FDA's regulations, given the FDA's clear intent not to preempt and the deference that must be given to local health and safety regulations).

157. *See* 21 U.S.C. § 355.

administration of it in Massachusetts.[158] The state cited the absence of an "abuse-resistant formulation," which "provoked concern that Zohydro ER may lead to opioid addiction and overdose fatalities, a concern especially potent given the recent spike in opioid- and heroin-related deaths in Massachusetts."[159] The drug's manufacturer Zogenix sued the state in federal district court, claiming that the emergency order was preempted by the FDA's approval of Zohydro.[160]

Initially, the court agreed with Zogenix and preliminarily enjoined the ban on the grounds that the state had "countermand[ed] the FDA's determinations and substitute[d] its own requirements . . . undermin[ing] the FDA's ability to make drugs available to promote and protect the public health."[161] Massachusetts responded by watering down its restrictions. First, Massachusetts required that physicians certify in a "Letter of Medical Necessity" that "other pain management treatments have failed" before prescribing Zohydro.[162] The district court enjoined this restriction, too, because it made "Zohydro a last-resort opioid" which "undeniably makes Zohydro less available" and thereby "presents a constitutional problem."[163] The court did so despite the fact that then-FDA Commissioner Margaret Hamburg called this particular restriction "consistent with the essential tenets of numerous medical society guidelines on appropriate pain management" and "precisely what responsible physicians should be doing."[164]

Subsequently, Massachusetts further revised its restrictions so that medical providers only needed to *consider* treatments other than Zohydro before prescribing it.[165] In the court's view, "[t]he obstacle—mandatory preliminary prescribing of other opioids—ha[d] now been removed."[166] If instead the regulation had required medical providers to prescribe Zohydro as a last resort—or not at all—it would have been preempted.[167]

The Zohydro saga implies that the difference between impermissible state regulation of drug safety and permissible state regulation of health and

158. Zogenix, Inc. v. Patrick, No. 14-11689, 2014 WL 1454696, at *1 (D. Mass. Apr. 15, 2014).
159. *Id.*
160. *Id.* at *1–2.
161. *Id.* (citing Geier v. Am. Honda Motor Co., 529 U.S. 861, 881 (2000)).
162. *See* Zogenix, Inc. v. Patrick, No. 14-11689, 2014 WL 3339610, at *2 (D. Mass. July 8, 2014) (quoting 243 MASS. CODE REGS. § 2.07(25)(d) (2024)), *vacated in part by Zogenix, Inc.*, 2014 WL 4273251 (D. Mass. Aug. 28, 2014).
163. *Id.* at *4.
164. *See* Catherine M. Sharkey, *States Versus FDA*, 83 GEO. WASH. L. REV. 1609, 1622 (2015) (citation omitted).
165. *See Zogenix, Inc.*, 2014 WL 4273251, at *3.
166. *Id.*
167. *See id.*

safety is one of degree, not of kind. Crucial to the preemption inquiry was whether the state's decision to ban an FDA-approved drug was grounded in the same concerns and evidence that the FDA expressly rejected (in which case preemption was warranted).[168] In effect the court in *Zogenix* reasoned that the FDA, in approving the drug despite its lack of an abuse-resistant formula, had considered the potential for abuse but concluded that the benefits of the drug outweighed its risks.[169] Yet the court did not seek input from the FDA—nor did it rely on the publicly available statement of then-Commissioner Hamburg—on the extent to which the various state-imposed restrictions were consistent with the agency's regulatory aims.[170] In our view, analyzing whether state regulations of FDA-approved drugs are preempted requires both.

The current moment compels us to turn this reasoning into a workable preemption framework. The Supreme Court's overruling of *Roe*[171] and *Casey*[172] in *Dobbs*[173] has transformed one-off prior clashes[174] into an issue of great national importance. *Dobbs* triggered laws that ban FDA-approved abortion medications, and other states have imposed various restrictions on the prescription and distribution of medication abortion pills, including bans on telemedicine appointments to prescribe the pills; bans on shipment through the mail; and informed consent requirements.[175] A new framework is needed to guide courts called upon to decide when FDA actions preempt state restrictions like these.

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168. *See* Sharkey, *supra* note 164, at 1628–29 (footnote omitted) ("The FDA deliberated on the precise health concerns that the state cited, and the agency's approval decision reflected a responsible risk-benefit analysis. Massachusetts's subsequent ban thus undermined the FDA's conclusions and, as such, posed a formidable obstacle to the federal regulatory scheme.").

169. *See id.* at 1628 n.83.

170. *Cf. id.* at 1624 (arguing that courts should give deference to the FDA's position on matters like those at issue in *Zogenix* so long as the "agency's position is supported by persuasive data or factual determinations").

171. Roe v. Wade, 410 U.S. 113 (1973).

172. Planned Parenthood of Se. Pa. v. Casey, 510 U.S. 1309 (1994).

173. Dobbs v. Jackson Women's Health Org., 597 U.S. 215, 231 (2022) (overruling *Roe* and *Casey*).

174. Professor Lars Noah has documented failed attempts by states to ban FDA-approved drugs. *See* Lars Noah, *State Affronts to Federal Primacy in the Licensure of Pharmaceutical Products*, 2016 MICH. ST. L. REV. 1, 16–19, 18 n.69 (describing failed attempts to ban and restrict the prescription or distribution of the morning-after pill and mifepristone (which failed on undue burden grounds)); *id.* at 19–22 (discussing, inter alia, how some states scheduled the muscle relaxant carisoprodol before the federal government did so in 2011, and how Minnesota in 2014 banned most uses of the antibacterial agent triclosan while specifically excluding products approved by the FDA for consumer use).

175. *See infra* Sections IV.A–B.

III. A NEW PREEMPTION FRAMEWORK

State law bans of FDA-approved drugs present unique challenges for implied preemption frameworks. On the one hand, these bans would seem to be a frontal assault on the FDA's primacy in regulating the safety and effectiveness of drugs, and one that threatens to upset the national market for pharmaceuticals. On the other hand, the states retain authority to regulate the practice of medicine, including restrictions on the prescribing and use of FDA-approved drugs. Moreover, the approval of a drug is not tantamount to mandating its sale or use within a given state.

The concurrent nature of state and federal regulatory authority over both the practice of medicine and abortion means that state-FDA clashes are destined for the courts. Even if Congress were to enact a new express preemption provision, courts would still need an interpretive framework to resolve the scope of preemption. That is, it is a question that courts can only answer with recourse to constitutional and administrative law norms. Considering that new legislation is highly unlikely, moreover, we stand on firm ground when we assert the need for courts to adapt preemption doctrine to this new reality.

Our proposed framework harnesses the "agency reference model" (designed to assist courts in deciding whether common law tort actions should be preempted) to scrutinize state regulations to ensure compatibility with FDA determinations about the safety and effectiveness of drugs. To withstand preemption, a state administrative or statutory restriction should reflect evidence either of new risks posed by drugs (in which case, we advocate a system akin to prior approval by the FDA) or that the regulation targets the same risks that the FDA identified in a complementary fashion (ideally, as confirmed by input from the FDA).

Our framework not only promotes national regulatory uniformity for an issue that Congress has addressed and that has large implications for the national economy, but—equally significantly—it harnesses the FDA's capacity to incentivize the generation of high-quality clinical data about drugs' safety and effectiveness. Our framework has distinct implications for the seemingly intractable political controversies surrounding medication abortion (including related Risk Evaluation and Mitigation Strategies (REMS) provisions), which we preview here and elaborate in Part IV.

A. Concurrent State-Federal Authority and the FDA

To date, scholars have wrestled with how to mediate conflicts between the FDA and the states but have not adequately accounted for the unique

challenges posed by state regulations—especially bans—of FDA-approved drugs. Such state regulations target areas of *concurrent* state and federal authority: the practice of medicine and abortion. We reject the notion of dual (or separate spheres) sovereignty whereby the states alone can regulate these areas and the federal government cannot. Rather, we argue that Congress can and does act in both domains.

Although Congress has the authority to enact new legislation expressly preempting state laws that contradict or deviate from FDA actions, it is exceedingly unlikely to do so. Therefore, courts will inevitably be called upon to adjudicate clashes between the states and federal administrative agencies in these areas of concurrent authority. Scholars have paid scant attention to judicial solutions in these realms. They largely agree that both the FDA and the states can regulate medication abortion. But they prefer Congress or the FDA itself to resolve these ambiguities and conflicts. Such legislative solutions will likely not materialize. Nor will further FDA actions obviate the need for courts to draw these lines. Our agency reference model, which is already built into implied preemption doctrine as it applies to products liability claims involving FDA-approved drugs and medical devices, can guide courts in their effort to enforce the Supremacy Clause while protecting federalism interests.

1. The Practice of Medicine

The states and the federal government can both regulate the practice of medicine. But there are aspects of the practice of medicine that are reserved to the states.[176] How should this play out in the context of state-FDA conflicts over pharmaceuticals?

The proviso oft-repeated by courts is that the power to regulate the practice of medicine is *traditionally* retained by the states *absent*

176. *See* Gonzales v. Oregon, 546 U.S. 243, 272 (2006) (interpreting the Controlled Substances Act (CSA) to limit the federal government's power to invalidate a state-approved medical practice (physician-assisted suicide) in accordance with the statute's "silence on the practice of medicine generally and its recognition of state regulation of the medical profession"); Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 449–50 (2015) ("[S]tates regulate medical practice by defining what falls within the scope of medical practice and requiring that those practicing medicine be licensed."); *id.* at 451 ("Although defining the scope of medical practice, licensing requirements, and medical board disciplinary actions are the primary ways that states regulate medical practice, there are a number of other ways in which states exert their authority to oversee medicine."). The FDA maintains that it does not regulate the practice of medicine. *See About FDA: Patient Q&A*, FDA, https://www.fda.gov/media/151975/download#:~:text=The%20FDA%20does%20not%20regulate,by%20health%20insurance%20or%20Medicare [https://perma.cc/465P-UVBK] ("The FDA does not regulate the practice of medicine, medical services, the price or availability of medical products and whether they are reimbursed by health insurance or Medicare.").

congressional will to the contrary.[177] That proviso takes on great significance in the realm of pharmaceuticals. Congress has created a national premarket approval system to regulate the safety and effectiveness of pharmaceuticals. Although it has not expressly preempted state laws to the contrary, it has created a program (REMS—elaborated on below) that allows the FDA to impose restrictions on the distribution of these drugs. Herein lies the rub, namely the overlap (or blurred line) between the practice of medicine and regulation of medical products. The availability of drugs to prescribe is no doubt related to "the practice of medicine," and no one seriously contests Congress's authority to vest in the FDA alone the power to determine which drugs can go to market. What about everything else?

Following conventional wisdom, Professor Myrisha Lewis argues that the states regulate the practice of medicine while the FDA regulates medical products.[178] Thus, for example, the FDA can regulate LASIK surgery machines and contact lenses, but not LASIK surgical techniques or the licensing of ophthalmologists.[179] Where the line between the practice of medicine and the regulation of a medical product is blurred, Lewis takes a cooperative federalism[180] approach and argues that the balance tips in favor of state regulation. In the context of what she terms life sciences techniques (including emerging technologies like gene editing and stem cell research), Lewis is wary of the FDA's acting outside its jurisdiction, treading on the states' police powers, and ultimately hindering innovation.[181] She thus lands on her preferred state regulatory approach.[182]

Although touted as cooperative federalism, Lewis's approach strikes us as more akin to a dual sovereignty model, seeking to allocate regulatory power between separate spheres. Lewis's primary concern seems to be about emerging techniques that might fall through the regulatory cracks should states be foreclosed from regulating. Regardless of the merits of such

177. *See, e.g.*, *Gonzales*, 546 U.S. at 275 (finding that the "*text and structure* of the CSA show that *Congress did not have [the] far-reaching intent* to alter the federal-state balance and the congressional role in maintaining it" (emphasis added)); Judge Rotenberg Educ. Ctr., Inc. v. FDA, 3 F.4th 390, 400 (D.C. Cir. 2021) ("[B]efore we would permit the FDA to dictate whether practitioners may administer [a type of] therapy to self-injuring and aggressive patients, we would *require an explicit statement from Congress to that effect*." (emphasis added)).

178. *See* Myrisha S. Lewis, *Halted Innovation: The Expansion of Federal Jurisdiction over Medicine and the Human Body*, 2018 UTAH L. REV. 1073, 1087.

179. *Id.* at 1088–89.

180. *See id.* at 1109 (arguing for a "cooperative regulatory apparatus"); Myrisha S. Lewis, *Innovating Federalism in the Life Sciences*, 92 TEMP. L. REV. 383, 390 (2020) (advocating a "cooperative framework draw[ing] on the concept of 'cooperative federalism'").

181. Lewis, *supra* note 178, at 1078. Lewis leans heavily on a 2017 report by the National Academies of Sciences, Engineering, and Medicine, when stating that "there are several aspects of biotechnology that do not fall within the current purview of federal jurisdiction." *Id.* at 1086.

182. *See* Lewis, *supra* note 180, at 402–10.

a framework in that specific context, it does not shed light on how to address state attempts to ban or restrict FDA-approved drugs.[183] For here too the line is blurred, as the restrictions that the FDA imposes on the prescription of certain medications through the REMS program straddle the line between federal and state jurisdictional spheres. The default "defer to the states" approach does not necessarily follow, given that it is emphatically clear that the FDA (and not the states) has the authority to approve or reject pharmaceuticals according to their safety and effectiveness.[184]

We join Professor Patricia Zettler in challenging this conventional wisdom that the states regulate the practice of medicine while the federal government regulates medical products.[185] The Constitution does not "require[] that the practice of medicine remain sacrosanct" and free of federal interloping.[186] In the context of state-FDA clashes over pharmaceuticals, Zettler has recognized that Congress can regulate not just the drugs themselves but aspects of their distribution, too.[187]

Exhibit A is the Risk Evaluation and Mitigation Strategy (REMS) statute, the validity of which has not been seriously questioned.[188] The REMS statute authorizes the FDA to impose certain restrictions, including those that infiltrate and regulate the traditional domain of the practice of medicine. These regulations cover the types of certification or training required for healthcare providers and pharmacies; the settings in which a drug can be dispensed; the documentation required to inform patients about safe-use conditions; and patient monitoring requirements.[189] The FDA can

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183. Indeed, Lewis herself concedes that states are not "permitted to overrule the FDA's approval of products, and historical state efforts to 'limit or entirely bar access' to contraceptives that were FDA approved, for example, have been invalidated by the Supreme Court." *Id.* at 401 (quoting Noah, *supra* note 174, at 16).

184. *See* 21 U.S.C. § 355.

185. Zettler, *supra* note 176, at 430; *see also id.* at 438 & n.54 (citing Linder v. United States, 268 U.S. 5, 18 (1925) ("Obviously, direct control of medical practice in the states is beyond the power of the federal government.")).

186. Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 KAN. L. REV. 149, 192 (2004).

187. *See* Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845, 886 (2017) (arguing that "the distinction between regulating medical practice and medical products is nebulous" because, as the Zohydro case demonstrates, "the FDA's preemptive reach can extend into medical practice regulation in certain circumstances").

188. Although plaintiffs have challenged the FDA's mifepristone REMS as invalid on procedural grounds, they have not asserted that the statute itself is unconstitutional or otherwise invalid.

189. *See* 21 U.S.C. § 355-1(f)(3); *see also* Zettler, *supra* note 176, at 462 ("The FDA's drug safety authority provides another example of how the agency indirectly regulates medical practice. The Food and Drug Administration Amendments Act of 2007 significantly strengthened the FDA's drug safety authority by, among other things, authorizing it to require [REMS] for certain drugs."); *id.* at 464 ("[W]hen a drug is subject to a REMS that includes elements to assure safe use, how practitioners use that drug is significantly affected by tasks that they must perform . . . [REMS] thus provide an additional example of the FDA indirectly regulating medical practice.").

impose REMS restrictions if the agency determines they are necessary to ensure a drug's benefits outweigh its risks.[190] These requirements must be "commensurate with the specific serious risk listed" on the drug's label.[191] And they cannot be "unduly burdensome on patient access to the drug, considering in particular . . . patients with serious or life-threatening diseases or conditions."[192]

In sum, REMS belies the dual sovereignty approach, whereby states and the FDA regulate in exclusive, separate spheres. Instead, in this realm, the states and the federal government have concurrent authority to regulate the practice of medicine as it relates to state-FDA conflicts over pharmaceuticals.[193]

2. Abortion

The Supreme Court in *Dobbs* held that "the authority to regulate abortion must be returned to the people and their elected representatives."[194] This devolution of authority away from courts to the people's elected representatives includes *federally* elected representatives. Justice Kavanaugh, in his concurrence, emphasized that abortion is now an issue "for the people and their elected representatives to resolve through the

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190. *See* 21 U.S.C. § 355-1(a)(1). When making this determination, the FDA considers the size of the population likely to use the drug; the seriousness of the disease or condition to be treated; the drug's expected benefits; the expected duration of treatment; the seriousness of the drug's known adverse events; and whether the drug is a new molecular entity. *Id.*

191. *Id.* § 355-1(f)(2)(A).

192. *Id.* § 355-1(f)(2)(C).

193. Professors Cohen, Donley, and Rebouché take this a step further to argue that Congress created the national premarket review system for drugs "to make approved drugs *accessible* (instead of just safe and effective)." David S. Cohen, Greer Donley & Rachel Rebouché, *The New Abortion Battleground*, 123 COLUM. L. REV. 1, 59 (2023) (emphasis added). They claim this purpose is "incorporated into the REMS statute . . . ." *Id.* at 59 & n.320 (citing 21 U.S.C. § 355-1(f)(2)(C) (noting that "elements to assure safe use" of a REMS-regulated drug "shall . . . not be unduly burdensome on patient access to the drug")). Their position—perhaps a strategic choice to avoid preemption arguments in order to minimize the potential impact on reproductive rights—may not withstand judicial scrutiny. Indeed, two federal district courts have rejected this interpretation of the REMS statute. *See* GenBioPro, Inc. v. Sorsaia, No. 3:23-0058, 2023 WL 5490179, at *6 (S.D.W. Va. Aug. 24, 2023) (concluding that the agency need only consider the effect on patient access of the REMS restrictions it wants to impose); Bryant v. Stein, No. 1:23-CV-77, 2024 WL 1886907, at *15 (M.D.N.C. Apr. 30, 2024) ("Congress does require the FDA to consider access and possible impacts on access when it implements and evaluates REMS elements for a drug. But nothing in the 2007 amendments makes the FDA responsible for generally ensuring access to all REMS drugs." (citation omitted)).

We note that our risk-centered, agency reference approach, which we set forth *infra* Section IV.A, would likely have a positive impact on patient access. Moreover, it is more likely to pass judicial muster. *See GenBioPro*, 2023 WL 5490179, at *10–11 (invalidating West Virginia's prohibition on prescribing mifepristone by telehealth).

194. Dobbs v. Jackson Women's Health Org., 597 U.S. 215, 292 (2022).

democratic process in the States *or Congress*."[195] Congress has enacted several laws regarding abortion,[196] which are presumptively valid exercises of Congress's commerce power.[197] *Dobbs* thus ought not to be interpreted as relegating abortion to the exclusive domain of the states.[198]

Indeed, post-*Dobbs* courts have stopped short of concluding that Congress *cannot* regulate abortion. Consider the ongoing litigation over an unsettled question of federal statutory interpretation, namely whether the Emergency Medical Treatment and Active Labor Act (EMTALA) requires hospitals to perform abortions in some circumstances and thereby preempts state laws that prohibit such abortions. The litigation is not concerned with whether Congress *can* regulate abortion but rather whether Congress in fact *did* regulate abortion through the statute. EMTALA requires that medical providers in Medicare-participating hospitals perform certain emergency medical procedures when a patient's health is in jeopardy.[199] The statute expressly "do[es] not preempt any State or local law requirement, except to the extent that the requirement directly conflicts with a requirement of this section."[200] After *Dobbs*, the Biden Administration's Department of Health and Human Services (HHS) issued guidance about EMTALA, directing that

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195. *Id.* at 338 (Kavanaugh, J., concurring) (emphasis added). True, the majority in *Dobbs* mentioned the "people's elected representatives" in the context of "26 States [having] expressly ask[ed] us to overrule *Roe* and *Casey*." *Id.* at 230; *see also id.* at 302 ("The Constitution does not prohibit the citizens of each State from regulating or prohibiting abortion. . . . We now . . . return that authority to the people and their elected representatives."). However, the majority's logic does not preclude Justice Kavanaugh's statement, especially in light of other presumptively valid federal laws governing abortion. *See infra* note 196.

196. *See, e.g.*, Freedom of Access to Clinic Entrances Act [FACE Act] of 1994, Pub. L. No. 103-259, 108 Stat. 694 (proscribing threatening or violent conduct meant to interfere with persons seeking to obtain or provide reproductive health services); Partial-Birth Abortion Ban Act [PBABA] of 2003, Pub. L. No. 108-105, 117 Stat. 1201 (banning the partial-birth abortion procedure).

197. *See* United States v. Wilson, 73 F.3d 675, 680 (7th Cir. 1995) (upholding the FACE Act on these grounds); *cf.* Gonzales v. Carhart, 550 U.S. 124, 169 (2007) (Thomas, J., concurring) ("I also note that whether the [PBABA] constitutes a permissible exercise of Congress' power under the Commerce Clause is not before the Court. The parties did not raise or brief that issue; it is outside the question presented; and the lower courts did not address it.").

198. *Cf.* Cohen, Donley & Rebouché, *supra* note 17, at 371–72 (arguing that strengthening the mifepristone REMS would leave "the agency vulnerable to accusations" that it is interfering with states' powers to set their own abortion policies (citing *Dobbs*, 597 U.S. at 302)).

199. *See* 42 U.S.C. § 1395dd(b). EMTALA defines "emergency medical condition" as "a medical condition manifesting itself by acute symptoms of sufficient severity . . . such that the absence of immediate medical attention could reasonably be expected to result in . . . placing the health of the individual (or, with respect to a pregnant woman, the health of the woman or her unborn child) in serious jeopardy." *Id.* § 1395dd(e)(1)(A)(i).

200. *Id.* § 1395dd(f).

physicians must provide an abortion when that is the necessary stabilizing treatment, and that contrary state laws are preempted.[201]

Thus far, in challenges to the Biden Administration's EMTALA guidance, courts (including the U.S. Supreme Court) have assumed that if Congress did in fact intend EMTALA to regulate abortion, this would have preemptive effect. No one contests whether the federal government *can* regulate in this area. When Texas sued the Biden Administration to enjoin enforcement of EMTALA in accordance with the HHS guidance, the courts held that EMTALA does not address abortion. But, as the Fifth Circuit noted, states' police powers over medical treatment is "not to be superseded *unless that was the clear and manifest purpose of Congress* . . . . Congress has not manifested that purpose in EMTALA."[202] Likewise, defending a challenge to its statute that criminalizes abortion, Idaho argued that EMTALA does not mention abortion, *not* that the federal government is powerless to regulate in this area.[203]

Whether Congress intended EMTALA to cover emergency abortion care is another issue the U.S. Supreme Court declined to address on the merits but is destined to work its way back to the high court. In a surprising turn of events, the Court granted certiorari on Idaho's emergency application but dismissed the petition as improvidently granted.[204] Nevertheless, six Justices offered insights into their views on the merits of the preemption issue. Justice Kagan (in a concurrence joined in relevant part by Justices Sotomayor and Jackson) declared that "[f]ederal law and Idaho law are in conflict about the treatment of pregnant women facing health emergencies" and "EMTALA unambiguously requires that a Medicare-funded hospital provide whatever medical treatment is necessary to stabilize a health

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201. *See* Letter from Xavier Becerra, U.S. Sec'y of Health & Hum. Servs., to Health Care Providers (July 11, 2022), https://www.hhs.gov/sites/default/files/emergency-medical-care-letter-to-health-care-providers.pdf [https://perma.cc/6QPT-L526].

202. Texas v. Becerra, 89 F.4th 529, 542–43 (5th Cir. 2024) (emphasis added) (citing Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996)). The United States has filed a petition for certiorari to the U.S. Supreme Court. See Petition for Writ of Certiorari, Becerra v. Texas, No. 23-1076 (U.S. filed Apr. 2024).

203. Emergency Application for Stay Pending Appeal at 14–16, Idaho v. United States, 144 S. Ct. 541 (2024) (No. 23A-470). Idaho nonetheless raised concerns that the Government's interpretation of EMTALA transformed emergency rooms into "federal abortion enclaves governed not by state law, but by physician judgment, as enforced by the United States's mandate to perform abortions on demand." Moyle v. United States, 144 S. Ct. 2015, 2021 (2024) (Barrett, J., concurring) (per curiam) (quoting Stay Reply Brief at 6, *Idaho*, 144 S. Ct. 541 (No. 23A-470)).

204. The U.S. Supreme Court granted Idaho's application for a stay of the Ninth Circuit's decision. *See Idaho*, 144 S. Ct. 541 (mem.) (staying the preliminary injunction issued by federal district court in Idaho and consolidating the cases for oral argument on the merits in April 2024). However, after briefing and oral argument on the merits, the Court dismissed the writ of certiorari as improvidently granted. *See Moyle*, 144 S. Ct. 2015.

emergency—and an abortion, in rare situations, is such a treatment."[205] Justice Alito (in a dissent joined in relevant part by Justices Thomas and Gorsuch) vehemently disagreed: "The text of EMTALA shows clearly that it does not require hospitals to perform abortions in violation of Idaho law."[206] Moreover, "EMTALA's narrow preemption clause . . . respects core state powers" and "signals that EMTALA's default position is coexistence with state law."[207]

The Court will ultimately decide whether EMTALA preempts state abortion laws.[208] But for now it is safe to conclude from the litigation to date, as well as the language of *Dobbs* and other presumptively valid federal laws governing abortion, that abortion remains an area of concurrent state and federal regulatory authority.

B. A Court-Centered Approach

How, then, should courts adjudicate conflicts between the states and the FDA in these areas of overlapping authority? Wary of empowering the same Court that handed down *Dobbs* to decide another abortion-related issue, and reacting to the trend (recently reinforced) against deference to federal agencies, scholars have shied away from a court-centered approach. But these issues will inevitably reach courts; moreover, with an appropriate framework in place, courts should be well positioned to adjudicate such conflicts.

First, some scholars argue that the Roberts Court will view an abortion-related preemption case as a contest between competing anti-abortion and

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205. *Moyle*, 144 S. Ct. at 2017, 2018 (Kagan, J., concurring); *see also id.* at 2026 (Jackson, J., concurring in part and dissenting in part) ("Idaho law prohibits what federal law requires, so to that extent, under the Supremacy Clause, Idaho's law is pre-empted." (citing Mutual Pharm. Co. v. Bartlett, 570 U.S. 472, 479–80 (2013))). Indeed, Justice Jackson would have gone further and decided the issue in the case at hand. *Id.* at 2023 ("The United States is still hamstrung in its ability to enforce federal law while States pass laws that effectively nullify EMTALA's requirements. . . . If anything, the need for a clear answer to the Supremacy Clause question has only increased in the intervening months.").

206. *Id.* at 2028 (Alito, J., dissenting).

207. *Id.* at 2034. The dissent took the further step of questioning whether a federal law enacted under the Spending Clause (such as EMTALA) could ever preempt a state criminal law or public health regulation—and suggested this was "yet another reason to be wary about interpreting EMTALA to displace the core powers of a nonconsenting State without unmistakable clarity regarding the meaning of federal law." *Id.*

208. Resolution of this issue may encompass not only statutory interpretation issues but also Congress's authority to use the Spending Clause to preempt state abortion laws. Justice Alito's dissent in *Moyle* telegraphed his view that "permitting preemption" of state criminal laws by this backdoor means goes too far. *Id.*; *see also id.* at 2020–21 (Barrett, J., concurring) (stating "it would be imprudent to answer the[] important question[] now"; namely "whether EMTALA, as a statute enacted under Congress's spending power and that operates on private parties, *can* preempt state law (an issue aired for the first time in this Court).").

pro-preemption tendencies, and the former will win the day.[209] We do not discount that possibility. But preemption often upends expectations about where the justices will land as a function of their ideological proclivities.[210] And it is likely as a descriptive matter that the Court—as the lower courts are doing—will need to decide the question whether federal law preempts state restrictions on FDA-approved drugs. When it does, it will need a preemption framework. We aim to construct one.

Second, scholars fear that the current Court's increasing resistance to deference to federal agencies will spill over into preemption. Professors Cohen, Donley, and Rebouché worry that "[i]f the FDA becomes actively involved in the preemption litigation, it could *transform* a case about a company's right to sell its FDA-approved product *into a case about government overreach*."[211] But courts have historically accorded a unique level of deference to the FDA's scientific expertise.[212] Although there is some risk that the medication abortion controversy could unsettle this record, we maintain that, even in a post-*Chevron* landscape, courts will continue to defer to the agency's well-reasoned scientific decision-making.[213]

Finally, scholars have advocated for agency actions and legislation to shore up the agency's preemptive authority. Unlike with respect to medical devices, there is no express preemption provision regarding state regulations of drugs. Legislation expressly preempting state bans or restrictions on medication abortion would obviate the need for courts to divine Congress's intent from the existing scheme.[214] But even these scholars concede that the prospects for such legislation are dim.[215] Professor Whelan nonetheless believes that new legislation is the best way to assert federal preemption

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209. *See* Whelan, *supra* note 16, at 197 ("Given the current majority's hostility toward abortion rights, the Court will likely conclude that federal law does not preempt such state bans or restrictions."); Cohen, Donley & Rebouché, *supra* note 17, at 378 ("[C]onservative justices have traditionally supported preemption based on federal food and drug law. And Chief Justice Roberts in particular might appreciate a perceived compromise where states must permit abortion through ten weeks completed with medication. But the Court that just overturned *Roe* may be unlikely to permit such a large exception to state abortion bans, especially if the scope of that exception is controlled by a government agency.").

210. *See* Sharkey, *The Administrative State and the Common Law*, *supra* note 135, at 1723–26.

211. Cohen, Donley & Rebouché, *supra* note 17, at 379 & n.425 (emphasis added) (citing Gillian E. Metzger, *The Roberts Court and Administrative Law*, 2019 SUP. CT. REV. 1, 2–3); Cohen, Donley & Rebouché, *supra* note 193, at 69 ("[T]he FDA's involvement in such litigation could divert attention from the drug manufacturer's claim and the business interests involved, allowing the Court to opine on agency overstep instead of the preemption issue, hampering the lawsuit more than helping it.").

212. *See supra* Section I.A.

213. *See supra* Section I.B.2.

214. *But see supra* note 208 (noting that the dissenting and concurring opinions in *Moyle* indicate that the U.S. Supreme Court may on another occasion decide the question whether Congress can use Spending Clause legislation to preempt state abortion laws).

215. *See* Cohen, Donley & Rebouché, *supra* note 193, at 53.

over state drug restrictions.[216] Accordingly she has proposed a detailed legislative solution that would amend the FDCA to prohibit states from banning FDA-approved drugs or contravening federal labeling and REMS requirements.[217] Short of new legislation, Whelan argues that the FDA could enact new regulations or issue new guidance to clarify its position on the issue.[218]

To adjudicate preemption disputes, courts must—and do—synthesize a discordant mix of existing statutory text, precedent, and normative principles to construct a workable framework. Even in a world where all nine U.S. Supreme Court justices are "textualists now,"[219] textualists routinely use substantive norms of statutory construction, particularly certain federalism canons, as background presumptions against which to interpret statutes.[220] Moreover, input from the relevant regulating federal agency has been a significant factor (whether explicitly acknowledged or not) governing courts' products liability preemption determinations.[221] Even Justice Thomas—the Court's leading skeptic of federal agencies' input on preemption[222]—authored a generic drug preemption decision in which he stated "[t]he FDA's views are 'controlling unless plainly erroneous or inconsistent with the regulation[s]' or there is any other reason to doubt that they reflect the FDA's fair and considered judgment."[223]

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216. *See* Whelan, *supra* note 16, at 203; *cf. id.* at 187–97 (arguing that existing statutory text and preemption doctrine does not resolve the issue of whether and to what extent states can restrict FDA-approved drugs).

217. *See id.* at 198.

218. *See id.* at 201.

219. *See* Harv. L. Sch., *The 2015 Scalia Lecture: A Dialogue with Justice Elena Kagan on the Reading of Statutes*, YOUTUBE, at 8:28 (Nov. 25, 2015), https://www.youtube.com/watch?v=DPEtszFT0Tg [https://perma.cc/F4ZQ-J7G8] ("I think we're all textualists now, in a way that just, you know, was not remotely true when Justice Scalia joined the bench."); *see also* Loper Bright Ents. v. Raimondo, 144 S. Ct. 2244, 2291 n.6 (2024) (Gorsuch, J., concurring) ("And as we like to say, 'we're all textualists now.'").

220. *See* Benjamin Eidelson & Matthew C. Stephenson, *The Incompatibility of Substantive Canons and Textualism*, 137 HARV. L. REV. 515, 564 & n.253 (2023) (citing Amy Coney Barrett, *Substantive Canons and Faithful Agency*, 90 B.U. L. REV. 109, 180 (2010) ("[T]he presumption against preemption is commonly justified as protecting the norm of federalism.")); Daniel J. Meltzer, *Preemption and Textualism*, 112 MICH. L. REV. 1, 7 (2013) ("[I]n an era in which textualist statutory interpretation has grown enormously in significance, a purposive approach to statutory interpretation remains powerful, indeed dominant, in preemption cases." (footnote omitted)).

221. *See* Sharkey, *Products Liability Preemption*, *supra* note 13, at 492 ("[T]he Court's reliance upon agency input [in products liability preemption jurisprudence] has often been *sub silentio*.").

222. Merck Sharp & Dohme Corp. v. Albrecht, 587 U.S. 299, 321 (2019) (Thomas, J., concurring) ("[N]either agency musings nor hypothetical future rejections constitute pre-emptive 'Laws' under the Supremacy Clause."); Wyeth v. Levine, 555 U.S. 555, 587–88 (2009) (Thomas, J., concurring) ("Congressional and agency musings, however, do not satisfy the Art. I, § 7, requirements for enactment of federal law and, therefore, do not pre-empt state law under the Supremacy Clause.").

223. PLIVA, Inc. v. Mensing, 564 U.S. 604, 613 (2011).

There can be no doubt that this interpretive process "poses issues of enormous complexity."[224] But it is one that courts must undertake, and we provide a framework to guide them.

C. The "Agency Reference Model"

We propose to harness the agency reference model—much like that used in implied preemption analyses (discussed *supra* Section II.B[225])—to assist courts in mediating clashes between the states and the FDA with regard to FDA-approved drugs. When the FDA determines that a drug is safe and effective for its intended use, it does so after analyzing detailed information (including data from three phases of clinical trials) relevant to that determination. When a state regulation of an FDA-approved drug is challenged, courts must analyze what the FDA specifically considered when it approved the drug. The agency reference model "'directs attention to a repository of agency information . . . focusing on the precise nature of the agency's regulatory cost-benefit (or risk-risk) determinations as well as the economic consequences of various determinations and the effects of state regulation on federal regulatory schemes.'"[226]

Under our approach, courts should let stand only those state restrictions that complement the FDA's goals of ensuring a drug's safety and effectiveness. State bans of FDA-approved drugs effectively contradict the agency's safety and effectiveness determinations. Short of a ban, precisely how far states *can* go depends on what the FDA has considered. Courts should evaluate the validity of a state regulation according to whether it complements or contravenes the FDA's risk-benefit calculus.

1. No Bans of FDA-Approved Drugs

Under our model, states cannot ban FDA-approved drugs. We reject arguments that states should be allowed to ban FDA-approved drugs due to

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224. Meltzer, *supra* note 220, at 38.

225. Preemption doctrine already reflects such an agency reference framework to assess whether state-law tort claims against drug manufacturers are impliedly preempted. Consider the impossibility preemption framework that the Supreme Court constructed in *Wyeth v. Levine*, 555 U.S. 555 (2009), and *Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299 (2019). Nor is this framework upended by the fall of *Chevron*, given that it is built on a *Skidmore* edifice. *See supra* note 135 (citing Sharkey, *Products Liability Preemption*, *supra* note 13, at 491–99) and accompanying text.

226. *See* Sharkey, *Federalism Accountability*, *supra* note 13, at 2153 (quoting Sharkey, *Products Liability Preemption*, *supra* note 13, at 485).

overlooked local conditions.[227] And we similarly reject claims that authorize states to enact such bans on moral grounds.[228]

Again, there is no express provision in the FDCA prohibiting state bans of FDA-approved drugs. Instead, our claim finds indirect support from the U.S. Supreme Court's analysis in *Mutual Pharmaceutical Co. v. Bartlett*, a decision that channeled the agency reference approach.[229] In *Bartlett*, the Court determined that a design defect claim (based on an inadequate warning) regarding a pain reliever was preempted because the manufacturer could not have unilaterally changed the drug's label without FDA approval.[230] In doing so, the Court expressly rejected the "stop-selling" rationale, i.e., the idea that a manufacturer can comply with both state and federal law by not making its product in the first place. According to the Court, this practice would be "incompatible with . . . pre-emption jurisprudence" and render the doctrine "all but meaningless."[231]

To be sure, FDA approval of a drug means that manufacturers *can* sell it in State A, not necessarily that they *must* be able to sell it in State A.[232] But the Supreme Court's reasoning in *Bartlett* takes this further step, explaining that the drug manufacturer could not comply with both federal law and state common law unless it stopped selling the drug; and the Court rejected the "stop-selling" theory as a valid escape from impossibility preemption. Moreover, the Court suggested the stop-selling argument applied a priori to state regulations, when it explained that common law duties *are akin to statutory mandates*.[233] The contrary view (raised emphatically by the

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227. *See, e.g.*, Thomas A. Costello, Note, *Quitting Cold Turkey?: Federal Preemption Doctrine and State Bans on FDA-Approved Drugs*, 26 WM. & MARY BILL RTS. J. 839, 840 (2018) (suggesting states should be able to ban an FDA-approved drug in certain limited conditions, including "a state's immediate local concerns reflecting unique, exigent circumstances"); Whelan, *supra* note 16, at 172 (arguing that state restrictions on FDA-approved drugs could have benefits in circumstances like the Zohydro case, in which the potent opioid was less safe and effective in a region particularly affected by the opioid crisis).

228. *Cf.* Jared C. Huber, Note, *Preemption Exemption: FDA-Approved Abortion Drugs After* Dobbs, 98 NOTRE DAME L. REV. 2217, 2251 (2023) (arguing that state bans and severe restrictions on FDA-approved drugs are not preempted if the state's purpose differs from the FDA's).

229. *See* Catherine M. Sharkey, *Field Preemption: Opening the "Gates of Escape" from Tort Law*, 50 J. LEGAL STUDS. S27, S43–S46 (2021) (situating *Bartlett* within the U.S. Supreme Court's embrace of the agency reference model, where courts "train[] their focus on the underlying regulatory record, with added input from the regulating agency as needed").

230. 570 U.S. 472, 475–76 (2013).

231. *Id.* at 488 (citation omitted).

232. *See id.* at 490 ("Federal law *requires* a very specific label for [the drug], and state law forbids the use of that label." (emphasis added)). By contrast, federal law does not explicitly *require* that manufacturers are able to sell a drug that the FDA has approved in a state that has forbidden it; it merely *allows* manufacturers to do so.

233. *See id.* at 491 ("[Statutory mandates] do precisely the same thing [as state common law duties]: They require a manufacturer to choose between leaving the market and accepting the

dissent) that state law requiring a manufacturer not to sell a drug in a state merely complemented federal law did not win the day.[234]

A more difficult issue arises when state bans on FDA-approved drugs are motivated by interests other than health and safety concerns.[235] And—as we elaborate below—restrictions short of a ban pose even more difficulties. To resolve these thorny issues, we urge courts to focus on whether state restrictions on FDA-approved drugs target the FDA's domain of safety and effectiveness—in other words, whether the restriction intrudes upon the FDA's determination that a drug is safe and effective for its intended use, as well as any restrictions (such as REMS) accompanying that determination. Thus, state-imposed restrictions targeting FDA-approved drugs—as opposed to procedures associated with drugs—are candidates for preemption; and, if they do not complement the FDA's determinations, then such restrictions cannot withstand preemption.

Total bans clearly target and subvert FDA determinations about drug approval and are therefore preempted. Even if a state decides to ban an FDA-approved drug not because it is unsafe but on, say, moral grounds,[236] such a ban subverts the FDA's power to do what Congress has authorized it to do. In other words, once something falls within the FDA's regulatory purview, a state is not at liberty to remove it. Moreover, as a matter of policy, courts should not permit this kind of bootstrapping logic because the primacy of an FDA-led premarket approval process has particular advantages in the realm of pharmaceuticals.[237]

To adjudicate restrictions short of a ban, we likewise urge courts to adopt a presumption that state regulations targeting FDA-approved drugs *are* regulations of the drugs' safety and effectiveness. Here, too, courts should focus not on the state legislature's purpose when it enacted a restriction on

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consequences of its actions (in the form of a fine or other sanction)." (citing Guido Calabresi & A. Douglas Melamed, *Property Rules, Liability Rules, and Inalienability: One View of the Cathedral*, 85 HARV. L. REV. 1089 (1972))). Professor Noah, too, has recognized that *Bartlett* could reach "entirely beyond tort litigation" by "suggest[ing] that FDA drug approval would impliedly preempt state positive law as well." Noah, *supra* note 174, at 34.

234. *See Bartlett*, 570 U.S. at 493 (Breyer, J., dissenting) ("A company can comply with both [state and federal law] either by not doing business in the relevant State or by paying the state penalty . . ."); *id.* at 501 (Sotomayor, J., dissenting) ("[I]t is clear that New Hampshire's design-defect claim did not impose a legal obligation that Mutual had to violate federal law to satisfy.").

235. *See* Sharkey, *supra* note 164, at 1628 n.85 ("A more difficult case would arise whereby the state asserted a different type of purpose or interest—one that was not directly contrary to the FDA's health and safety determination. . . . In such a case, the purpose behind the federal regulations would be different from the state's motivation for action, and the FDA ostensibly would not have considered the state's (non-health and safety) related purposes when regulating.").

236. *See* Huber, *supra* note 228, at 2251.

237. *See infra* Section III.D (setting forth policy arguments in favor of FDA-led pharmaceutical regulation).

an FDA-approved drug—which would reify a dual sovereignty approach in an area of concurrent state and federal authority—but rather on whether the FDA considered, enacted, and/or rejected that very restriction. In other words, courts should adopt a risk-centered approach, anchored in the agency reference model. Thus, if a state regulation targets an FDA-approved drug, any otherwise legitimate state concerns regarding it are, for purposes of adjudicating disputes between the states and the FDA, tantamount to concerns about the drug's safety and effectiveness. Such a presumption encourages states to consider what the FDA evaluated before enacting restrictions on FDA-approved drug, and is necessary for the FDA to retain its dominion over drug safety and effectiveness.

That is not to say that states are powerless to assert their interests in either regulating abortion or the practice of medicine related to an FDA-approved drug. States, however, must do so in a way that is *subordinate* to the FDA's safety and effectiveness determination. That is why state regulations that *target* FDA-approved drugs fall under this presumption whereas, on the contrary (and as we elaborate below), states may regulate issues—such as a drug's effects on public health—that fall outside the FDA's regulatory domain.[238]

2. Addressing New Risk Evidence

Courts should allow state regulations that complement FDA decisions by addressing new risk evidence that the agency has not addressed. We consider in turn state regulations of FDA-approved drugs that address either (1) risks of a *different type or greater severity* than the FDA previously considered or (2) *in complementary fashion*, the *same* risks that the FDA has already identified. Along the way, we extract principles from existing FDA regulations and implied preemption doctrine in the context of state-FDA conflicts.

a. Different Risks

Courts have allowed state-law tort claims that address new risk evidence that the FDA has not considered.[239] They should do the same when assessing

238. *See infra* Sections IV.B–C (discussing preemption with respect to issues that are orthogonal to drug safety and effectiveness).

239. Under the "Changes Being Effected" (CBE) provision, manufacturers can change labels without FDA approval if they have "newly acquired information." 21 C.F.R. § 314.70(c)(3), (c)(6)(iii) (2024). If a state-law claim against a manufacturer addresses newly acquired information and addresses a design or labeling change that a manufacturer may unilaterally make without FDA approval, then there may be no preemption of that claim. *See* Wyeth v. Levine, 555 U.S. 555, 568–69 (2009).

state regulations. What amounts to new risk evidence? According to FDA regulations, "newly acquired information" is:

> [D]ata, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.[240]

Moreover, the FDA's regulation only allows new analyses of previously submitted data to count as newly acquired information if they "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA."[241]

States (just like plaintiffs in tort suits) should not be permitted to offer information previously analyzed by the FDA as evidence of different or greater risks. Under existing conflict preemption doctrine, plaintiffs' tort claims are preempted when their purported newly acquired information "reflects information—for all intents and purposes—that was provided to the FDA at the time of the [drug's] initial approval."[242] Such data do not reveal new risks, and therefore claims based thereon cannot withstand preemption. Crucially, courts have found that modifications to drug labels according to the "Changes Being Effected" (CBE) provision—which allows manufacturers to change labels without FDA approval if they have "newly acquired information"[243]—presuppose the *existence* of new risk information.[244] That is why a "state law duty to initiate such a change is . . . not by its nature a second guess of an FDA judgment."[245] In practice, that means newly acquired information must not be litigation-driven.

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240. 21 C.F.R. § 314.3(b) (2024).

241. *Id.*; *see also* Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603, 49607 (Aug. 22, 2008) (to be codified at 21 C.F.R. pts. 314, 601, 814) ("If a sponsor submits information to FDA, then later conducts a new analysis that demonstrates that labeling should be revised to account for that information, a CBE would be appropriate.").

242. Ridings v. Maurice, 444 F. Supp. 3d 973, 993 (W.D. Mo. 2020); *see also In re* Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prod. Liab. Litig., 185 F. Supp. 3d 761, 769 (D.S.C. 2016); Gibbons v. Bristol-Myers Squibb Co., 919 F.3d 699, 708 (2d Cir. 2019); McGrath v. Bayer HealthCare Pharms. Inc., 393 F. Supp. 3d 161, 167–71 (E.D.N.Y. 2019).

243. 21 C.F.R. § 314.70(c)(6)(iii) (2024).

244. *In re* Celexa & Lexapro Mktg. & Sales Pracs. Litig., 779 F.3d 34, 41 (1st Cir. 2015).

245. *Id.* (citing Wyeth v. Levine, 555 U.S. 555, 578–79 (2009)); *see also id.* ("[T]he line so drawn lets the FDA be the exclusive judge of safety and efficacy based on information available at the commencement of marketing, while allowing the states to reach contrary conclusions when new information not considered by the FDA develops.").

Plaintiffs cannot "create their own 'newly acquired information' through the use of experts."[246]

When states want to impose restrictions on FDA-approved drugs based on new risk evidence, one approach would be for states to mount a direct challenge to the FDA's approval decision or subsequent action on a drug (as described in Section I.A.1, *supra*). In our view, this would be preferable to an indirect challenge via enacting state positive law, in the sense that it would authorize courts to examine the regulatory record before the FDA in order to determine whether the agency failed to consider a new or greater risk.

A more favorable approach (and perhaps more feasible as well, in light of various standing and ripeness issues states could face in mounting direct challenges[247]) would be for courts to require that states submit such new risk evidence *to the FDA* for prior approval before enacting state regulations.[248] Courts could look to the principles embodied in the existing Prior Approval Supplement (PAS) process, which requires that sponsors submit major changes to the FDA *for prior approval*.[249] In contrast to the CBE provision—which, again, allows manufacturers to change labels unilaterally if they have "newly acquired information"[250]—the FDA requires PAS for "major changes," including changes to the drug's substance or production process with the "substantial potential to have an adverse effect on the . . . safety or effectiveness of the drug";[251] labeling changes other than

246. R.S.B. *ex rel.* Hammar v. Merck & Co., No. 20-C-1402, 2021 WL 6128161, at *4 (E.D. Wis. Dec. 28, 2021); *see also* R.S.B. *ex rel.* Hammar v. Merck & Co., No. 20-C-1402, 2022 WL 3927868, at *4–5 (E.D. Wis. Aug. 31, 2022) (finding that neither the plaintiff's expert's reanalysis of previously known data nor an academic article reporting on an adverse event associated with the drug counted as "newly acquired information" within the meaning of § 314.3(b)).

247. The U.S. Supreme Court rejected various theories of standing in the challenge to the FDA's loosening of mifepristone restrictions. *See* FDA v. All. for Hippocratic Med., 602 U.S. 367, 396 (2024) (dismissing the challenge on standing grounds); *id.* at 390 (rejecting doctor plaintiffs' theory of "conscience injury"); *id.* at 392 (rejecting what it termed the doctors' theory of "doctor standing" which would "essentially allow any doctor or healthcare provider to challenge any FDA decision approving a new drug"); *id.* at 394–95 (rejecting the Alliance's theory of associational standing); *see also* Jonathan H. Adler, *Who Can Sue the Food and Drug Administration?*, VOLOKH CONSPIRACY (Apr. 2, 2024, 12:50 PM), https://reason.com/volokh/2024/04/02/who-can-sue-the-food-and-drug-administration [https://perma.cc/AXC7-5Z7S] (noting that historically it has been difficult for parties not regulated by the FDA to assert standing to sue the agency for its regulatory and drug approval decisions).

248. FDA approval of a proposed state regulation would likely be a function of both the merits of the new risk evidence that a state submits and how the regulation would impact national regulatory uniformity. For example, a proposed regulation that would change a drug's label would have a greater effect on national uniformity (because manufacturers would need to change the label on the drug they sell nationwide) than would a proposed regulation governing who, in a particular state, can prescribe a drug and under what conditions.

249. 21 C.F.R. § 314.70(b) (2024).

250. *Id.* § 314.70(c)(6)(iii).

251. *Id.* § 314.70(b)(1).

those covered by the CBE regulation;[252] and changes made to address "significant questions regarding the integrity of the data supporting [the drug's original drug approval application]."[253] Prior to distributing a drug reflecting such a change, manufacturers must submit to the FDA a "detailed description of the proposed change[s]," including the "methods used and studies performed to assess the effects of the change" and "[t]he data derived from such studies."[254] As Justice Alito—citing an FDA amicus brief—noted in his *Albrecht* concurrence, the FDA has historically accepted PAS applications instead of CBE supplements "where significant questions exist on whether to revise or how to modify existing drug labeling."[255] Moreover, a PAS submission and the FDA's response (or lack thereof) can be determinative in preemption analysis.[256]

To be sure, PAS and CBE regulations do not apply to states; they apply to drug manufacturers. But the U.S Supreme Court decided that CBE and PAS procedures were key to determining whether a state-law tort claim is preempted in *Wyeth* and *Albrecht*.[257] And the Court might fashion, as a matter of administrative common law, an analogous framework to govern preemption of state positive law. Preemption of state regulations of FDA-approved pharmaceuticals based on different or greater risks is necessarily the domain of federalism values, and there are strong normative arguments (discussed in Section III.D, *infra*) in favor of implementing an agency reference model in this context.

b. Same Risks

State regulations based on the same risks considered by the FDA threaten to undermine the agency's risk-benefit analysis, unless these regulations are truly complementary. To make this determination, courts must determine what risks the FDA has identified; what restrictions it has accordingly imposed; and whether the state regulation in question complements that calculus.

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252. *Id.* § 314.70(b)(2)(v).

253. *Id.* § 314.70(b)(2)(viii).

254. *Id.* § 314.70(b)(3). Applicants can request that the FDA expedite its review for reasons relating to public health or extreme hardship. *See id.* § 314.70(b)(4).

255. Merck Sharp & Dohme Corp. v. Albrecht, 587 U.S. 299, 326 (2019) (Alito, J., concurring) (quoting Brief for United States as Amicus Curiae Supporting Petitioner, *Albrecht*, 587 U.S. 299 (No. 17-290)).

256. *See, e.g.*, *In re* Zofran (Ondansetron) Prods. Liab. Litig., 541 F. Supp. 3d, 164, 204 (D. Mass. 2021) ("Indeed, if GSK had . . . submitted the 2020 PAS, it would be clear that plaintiffs' claims would be preempted based on the FDA's response to that PAS.").

257. *See supra* notes 219–24 and accompanying text (discussing the federalism norms and agency input, in addition to cannons of statutory interpretation, that animate implied preemption doctrine in the FDA context).

How should courts do this? Here we draw from the FDA's position on the interaction between a proposed CBE supplement and the REMS requirements for a given drug. In the FDA's view, if the agency imposes warnings consistent with a drug's REMS to ensure that the drug's benefits outweigh its risks, a CBE supplement can *strengthen* warnings related to the risk that the *FDA has identified*.[258]

Likewise, in our proposed framework, the FDA leads while the states must follow. The FDA conducts a risk-benefit analysis of a drug, and the states can enact regulations in service of that calculus. If the FDA has imposed REMS restrictions on a drug, then there is a convenient benchmark against which to measure whether a state regulation upsets the agency's risk-benefit analysis.

But the FDA's risk-benefit analysis will not always be so explicit. We recognize that it might be difficult for courts to determine whether the FDA would have approved a state restriction if there is no evidence in the record or legislative history about a similar one. In that case, courts may seek the FDA's input.[259] To return to the Zohydro example, recall that the then-Commissioner of the FDA considered the state's imposition of certain prescribing restrictions as in accord with the FDA's public health mission. We do not mean to suggest that courts should take the FDA's say-so to have preemptive effect. When courts solicit the FDA's input on whether a state regulation upsets its risk-benefit analysis, the agency must support its view with empirical evidence.

D. Advantage FDA

In applying the agency reference model to resolve conflicts between the states and the FDA by allowing only those state regulations that complement the FDA's determinations, we enter contentious federalism

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258. Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices 73 Fed. Reg. 49603, 49607 (Aug. 22, 2008) (to be codified at 21 C.F.R. pts 314, 601, 814) ("If [a drug's] sponsor became aware of newly acquired safety information that would otherwise be appropriate for a CBE, but would require the sponsor to modify an element to assure safe use that is required under a REMS, *the sponsor would need to receive prior approval of the labeling change*. However, if the newly acquired information is related to the concern leading to a REMS *but the proposed change to labeling could be made without requiring a modification of the REMS*, the approved labeling for the product could be strengthened *without prior approval*." (emphasis added)).

259. *See* Catherine M. Sharkey, *Federalism in Action: FDA Regulatory Preemption in Pharmaceutical Cases in State Versus Federal Courts*, 15 J.L. & POL'Y 1013, 1037–40 (2007). Alas, historically, state courts have been less apt to seek the FDA's input. *See id.* at 1038; *see, e.g.*, Risperdal & Invega Cases, 263 Cal. Rptr. 3d 412, 426 (Cal. Ct. App. 2020) (rejecting defendant's argument that the FDA's statement in a reply brief in unrelated litigation was clear evidence that the FDA would have rejected a CBE submission, and deeming it "of little value" in determining whether the requirements of *Albrecht* had been met).

debates. Specifically, in the realm of pharmaceuticals, our framework advantages FDA-led regulation in order to promote national uniformity of drug regulation and harness the ability of the FDA to generate safety-critical information. In this way, our preemption framework is a normative one, grounded in significant public policy considerations.

1. Promoting a Uniform National Market

As a general matter, regulating products which are marketed, sold, and distributed nationally via state law presents a threat of spillover effects that risk upending a uniform national market.[260] These effects can export externalities onto other states. This risk applies with even greater force to drugs, the safety and effectiveness of which the FDA *must* evaluate (at the national level) before they can enter the market.[261]

Some scholars are more welcoming of balkanization. Professor Heather Gerken and Ari Holtzblatt have argued that the spillovers associated with state-by-state regulation grease the wheels of democracy.[262] Spillovers "put issues on the national agenda, convert inchoate majorities into cohesive ones, and overcome congressional gridlock. They also enlist state politicians and their constituents in the project of pluralism, forcing state officials to engage and state citizens to take their democratic lumps."[263] As such, spillovers power the engine of politics and policymaking by "prod[ding] state policymakers into action, forcing political elites to debate policies they'd rather ignore or solve problems they'd rather not address."[264] In the interest of preserving our federalist democracy, they say, sometimes we need to "take our lumps and live under a policy we don't like."[265]

We take the point that spillover effects might be desirable in some contexts, especially regarding issues that are not politically salient or which Congress has not addressed. But this point loses its force in the context of state bans of FDA-approved drugs. Gerken and Holtzblatt themselves concede that courts should intervene to stop "high-cost, low-salience"

260. *See* Samuel Issacharoff & Catherine M. Sharkey, *Backdoor Federalization*, 53 UCLA L. REV. 1353, 1382–89 (2006) (arguing that the law of products liability, though based in state substantive law, is particularly prone to spillover effects because products are made, distributed, and sold for a national market); *id.* at 1385 (explaining that interests in national uniformity are particularly high, and interests in state sovereignty are comparatively low, in the realm of products liability, as "most products are mass produced and mass distributed, without any clear sense of where in the national market they might end up").

261. *See* 21 U.S.C. § 355(a).

262. Heather K. Gerken & Ari Holtzblatt, *The Political Safeguards of Horizontal Federalism*, 113 MICH. L. REV. 57, 81 (2014).

263. *Id.* at 90.

264. *Id.* at 93.

265. *Id.* at 104.

spillovers, which generate more national economic harms than democratic benefits.[266] In our view, the potential national economic impact of, say, twenty state bans on an FDA-approved drug would outweigh any democratic benefits gained by allowing state legislatures to debate the safety and effectiveness of a drug that the FDA already decided was safe and effective, regardless of whether this was carried out pursuant to states' authority to regulate the practice of medicine, morality, or something else.[267]

Professor Roderick Hills has attacked national uniformity arguments from another angle. He is especially wary of courts' ability to determine which level of government should regulate which issue.[268] And he has critiqued arguments in favor of preemption on the basis of cost-externalization for failing to recognize that Congress, too, is capable of externalizing costs. Given this, "courts should not attempt to correct state parochialism until they make some comparison of the inefficiencies of state cost exporting with the inefficiencies of federal gridlock."[269]

Again, while Hills's argument may be well taken in certain contexts, it does not give us pause here in the context of the regulation of FDA-approved drugs, a (perhaps rare) area of congressional activity.[270] This stands in contrast to areas like food labeling. As one federal district court found when assessing the validity of Vermont's requirement that genetically engineered foods be so labeled, the regulation of food and beverages is "an area in which Congress has long expressed its awareness of state legislation and has consistently tolerated the states' competing interests and regulatory control."[271] The existence of a scheme of complementary state regulations might explain why "[t]he FDA's food and food labeling regulations are far less comprehensive than those applicable to prescription drugs."[272]

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266. *Id.* at 107.

267. If a critical mass of states were to ban an FDA-approved drug, it would threaten to upset the pharmaceutical industry, which is based on a national manufacturing and distribution system. *See* Brief for the Pharmaceutical Research and Manufacturers of America as *Amicus Curiae* in Support of Petitioners at 30, FDA v. All. for Hippocratic Med., 602 U.S. 367, 396 (2024) (Nos. 23-235 & 23-236) (arguing that the Fifth Circuit inappropriately dismissed concerns about the potential for its decision to destabilize the pharmaceutical industry because, "even though the Fifth Circuit limited its holding to supplemental actions, its underlying reasoning could apply with equal force to initial approvals, thus risking" discord and potentially stifling innovation).

268. *See* Roderick M. Hills, Jr., *Against Preemption: How Federalism Can Improve the National Legislative Process*, 82 N.Y.U. L. REV. 1, 6 (2007).

269. *Id.* at 27.

270. *See supra* Section II.A (discussing Congress's steady nationalization of drug regulation).

271. Grocery Mfrs. Ass'n v. Sorrell, 102 F. Supp. 3d 583, 617, 617 n.25 (D. Vt. 2015), *appeal withdrawn by* No. 15-1504, 2016 WL 11785969 (2d Cir. Aug. 5, 2016); *see also* 21 U.S.C. § 337(b) (allowing states to enforce violations of food labeling provisions so long as states give adequate notice to the federal government and/or the federal government is not prosecuting the same action).

272. *See* Sharkey, *supra* note 164, at 1629, 1629 n.87.

In sum, Congress has created a *federal* premarket approval system for drugs in response to what it has perceived, time and again, to be an issue of *national* import.

2. Harnessing the FDA's Capacity to Generate Information

As discussed above, by limiting state-level lawmaking to that which complements the FDA's determinations about safety and effectiveness, our model avoids a proliferation of balkanized, conflicting state and federal regulations. Here we explore an additional (often overlooked) benefit of the FDA's prioritized status: As a matter of public health and safety, the FDA's approval process generates vital first-hand, first-rate clinical data about the safety and effectiveness of drugs.[273]

Professor Rebecca Eisenberg was the first to draw attention to this aspect of how FDA regulation promotes the generation of such high-quality clinical data.[274] Drug manufacturers perform "scientific investigation of a particular sort—specifically, the conduct of scientifically rigorous clinical trials of drugs."[275] Absent FDA regulation, which generates "[e]mpirically tested knowledge about [drugs'] effects in patients," drug manufacturers would be incentivized to produce only such information as suits their bottom line.[276]

Although state legislatures might hold hearings to gather adequate data before enacting a law, they are not poised to evaluate the safety and effectiveness of drugs such that medical providers and patients will trust their scientific judgment. As a matter of institutional design, legislatures can enact laws based on information that a federal court would deem insufficient to withstand a procedural challenge to final agency action. State legislatures' decisions to ban or approve drugs are not based on scientific judgment in any enforceable way. It is generally not the business of the

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273. We explore below, in the context of bans on gender-affirming care for minors, how state legislatures' assessment of drug safety and effectiveness can be based entirely on second-hand, second-rate data. *See infra* Section IV.C.

274. *See* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMMS. & TECH. L. REV. 345 (2007). Contrary to the common criticism that FDA regulation of drugs stifles innovation, Eisenberg claims that it "*promot[es]* a valuable form of pharmaceutical innovation—the development of credible information about the effects of drugs. . . . [T]oday drug regulation guides the development of information that turns poisons, used advisedly, into drugs." *Id.* at 347.

275. *Id.* at 373; *see also id.* at 373–80 (discussing in more detail the type of information that FDA regulation generates and the incentives of manufacturers to produce such information).

276. *See id.* at 347; *see also id.* at 385–86 (dismissing the argument that private firms could fill the FDA's certification function, as the firms with the most scientific expertise might have conflicts of interest that would "call[] into question the trustworthiness of the review. . . . Scientific credibility is difficult to establish and fragile to maintain, cautioning against radical departure from a system that enjoys some current credibility").

legislature, under the auspices of its plenary police powers, to justify its decision-making on scientific grounds.

Don't just take it from us. In an amicus brief advocating in favor of the Supreme Court's grant of certiorari in the *Alliance for Hippocratic Medicine* case, more than 600 state legislators claim they "rely on the FDA's determination of whether a pharmaceutical drug is approved for distribution in the United States, and then regulate from that baseline to make healthcare accessible based on their constituents' needs and preferences."[277] The FDA's Center for Drug Evaluation and Research, staffed by highly trained scientists, carries out the agency's mandate to determine whether drugs are safe by weighing their risks against their benefits.[278] Legislators depend on the FDA's expertise because "most states would never have the resources to address [drug safety] themselves."[279] States play a "*complementary* role by legislating to expand or tailor their constituents' access to an FDA-approved medication."[280]

In sharp contrast, it is emphatically the FDA's business to justify its decisions about drug safety and effectiveness on scientific grounds. Moreover, the years-long FDA New Drug Application (NDA) approval process is specifically designed to *generate* clinical data about the safety and effectiveness of drugs according to scientific expertise. FDA approval is "contingent upon satisfaction of a standard for safety and efficacy [rather than] merely upon submission of data."[281] We have tailored our preemption framework to harness the FDA's unique power to *generate* this crucial data.

IV. CONTEMPORARY APPLICATIONS

We put our framework to the test by applying it to a highly contentious contemporary issue: state abortion regulations. Under our agency reference model, states can enact regulations that complement the FDA's risk analysis, embodied by the mifepristone REMS. Restrictions that subvert that calculus, such as bans of abortion-inducing drugs or telehealth proscriptions, cannot withstand preemption. The flip side of our model (and a key limitation of it), given its focus on the FDA's risk-benefit analysis with respect to *drug* safety and effectiveness, is that *general* abortion bans

277. Brief of Over 600 State Legislators as *Amici Curiae* in Support of Petitioners at 3, FDA v. All. for Hippocratic Med., 602 U.S. 367, 396 (2024) (Nos. 23-235, 23-236).

278. *See id.* at 8–11; *see also id.* at 22–23 ("By mandate, the FDA assembles expert teams to weigh the evidence. . . . States have no comparable dedicated teams to weigh drug safety and efficacy, nor could many states readily assemble such teams.").

279. *Id.* at 11.

280. *Id.* at 25 (emphasis added).

281. Eisenberg, *supra* note 274, at 385.

that do not target the FDA's safety-and-effectiveness decisional domain are not preempted. Finally, a corollary of our model is that when the agency has not acted, state regulations of drug safety are not preempted. States can fill the void of FDA inaction, either with gap-filling drug safety regulation, or—as the proliferation of gender-affirming care bans shows—the bootstrapping of politically-motivated decisions under the guise of health and safety concerns.

A. The Model's Promise: Reconciling REMS and State Medication Abortion Restrictions

At the outset, we highlight once again the distinction between direct and indirect challenges to FDA actions in the realm of medication abortion. The FDA's approval of mifepristone, and subsequent restrictions that the agency imposed on the drug through REMS, are the subject of ongoing *direct* challenges that the FDA acted in an arbitrary and capricious manner.[282] Here we take up the distinct issues raised by state laws that pose *indirect* challenges to both the FDA's approval of mifepristone and the REMS restrictions imposed on the drug. We are not the first to posit that REMS restrictions may affect preemption analysis.[283] But we are the first to propose a model to help courts determine precisely which state restrictions are preempted, and which are not.

The current mifepristone REMS requires that healthcare providers who prescribe the drug and pharmacies that distribute it be specially certified, and that patients sign a Patient Agreement Form documenting the conditions of safe use.[284] As the FDA removed the in-person dispensing requirement, the REMS allows for the prescription of mifepristone via telemedicine and

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282. *See supra* Section I.B.2.

283. *See* Whelan, *supra* note 16, at 198 n.396 (noting, in the context of advocating for new legislation expressly preempting state restrictions on FDA-approved drugs, that "[t]he case for preemption is arguably stronger when a drug has a REMS because it illustrates an extensive consideration of the drug's risks, benefits, and related safety measures"); Cohen, Donley & Rebouché, *supra* note 17, at 376 ("Because Congress seemed to demand that the FDA provide both the ceiling and the floor of regulation when issuing a REMS, there is a strong argument that states cannot regulate a REMS product differently than the FDA.").

284. *See* FDA, 5103833, RISK EVALUATION AND MITIGATION STRATEGY (REMS) SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200MG 1, 3–4 (2023), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2023_01_03_REMS_Full.pdf [https://perma.cc/FSF5-VSFQ].

dispensing through the mail.[285] States have enacted various additional restrictions.[286]

Our proposed agency reference model provides guidance to courts in deciding preemption challenges to these state laws. First, courts should recognize the primacy of FDA authority in this realm. Next, courts should recognize that REMS restrictions stand in for the FDA's risk-benefit analysis, which states must not undermine.[287] In practice this means that states cannot enact restrictions that are at odds with the goals of a drug's REMS. Thus, if the FDA determines that providers can prescribe mifepristone through telemedicine, a state cannot prohibit telemedicine prescription. For instance, West Virginia requires—in direct contradiction of the 2023 REMS—that mifepristone not be prescribed via telemedicine.[288] A West Virginia federal district court's determination that this restriction amounts to "impossibility preemption"[289] aligns with our model.

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285. In April 2021, the FDA said it intended to exercise enforcement discretion with respect to the then-existing in-person dispensing requirement during the COVID-19 public health emergency. In December 2021, the agency announced that it would require a REMS modification to remove the in-person dispensing requirement from the mifepristone REMS. It approved the supplemental REMS applications of mifepristone's brand-name and generic manufacturers in January 2023. Since it exercised enforcement discretion with respect to the in-person requirement in the interim, the FDA has effectively allowed the dispensing of the pill via telemedicine since 2021. *See Questions and Answers on Mifepristone*, *supra* note 1; *see also* CTR. FOR DRUG EVALUATION & RSCH., APPROVAL PACKAGE FOR: APPLICATION NUMBER: 020687ORIG1S025 (2023), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/020687Orig1s025.pdf [https://perma.cc/NDT4-5FEE].

286. *See* Grossman & Cortez, *supra* note 6 (manuscript at 36) (cataloging state restrictions on mifepristone that deviate from FDA conditions of approval, including sixteen states that require physicians to prescribe it; nine that ban telehealth prescriptions; two that require the first dose to be taken in the presence of a physician; and two that ban the mailing of abortion pills).

287. REMS restrictions must also "not be unduly burdensome on patient access to [a] drug." 21 U.S.C. § 355-1(f)(2)(C). Whereas our framework centers on the primacy of the FDA's safety-and-effectiveness domain, other scholars have emphasized a national mandate to make drugs accessible. *See supra* note 193; *see also* Brief for Food and Drug Law Scholars and Professors as *Amici Curiae* Supporting Petitioners and Reversal at 6, FDA v. All. for Hippocratic Med., 602 U.S. 367 (2024) (Nos. 23-235 & 23-236) (arguing that the REMS restrictions are required to be the "*least restrictive necessary* to ensure that the drug's benefits outweigh its risks").

288. *See* W. VA. CODE § 30-3-13a(g)(5) (2022) ("A physician or health care provider may not prescribe any drug [via telemedicine] with the intent of causing an abortion."); *id.* § 30-1-26(b)(9) (2022) (prohibiting telehealth practitioners from "prescribing or dispensing an abortifacient"). The provisions of West Virginia law that prohibit prescribing medication abortion pills predate the Unborn Child Protection Act (UCPA). *Compare id.* § 30-3-13a(g)(5) (2022) (effective June 7, 2019), *with id.* §§ 16-2R-1 to -9 (2022) (effective Sept. 13, 2022).

289. GenBioPro, Inc. v. Sorsaia, No. 3:23-0058, 2023 WL 5490179, at *11 (S.D.W. Va. Aug. 24, 2023). The court recognized that Congress had allocated authority to the FDA to "dictate[] the manner in which mifepristone may be prescribed." It reached this conclusion on statutory interpretation grounds. *Id.* ("This is a determination which Congress has allocated to the FDA."). The court cited 21 U.S.C. § 355-1(f)(3)(C), which provides that REMS restrictions may specify that "the drug be dispensed to patients only in certain health care settings, such as hospitals." *See also id.* ("The FDA has evaluated the criteria Congress designated and has come to the reasoned conclusion that that mifepristone may be

Consider in a similar vein a rule enacted in South Dakota requiring that, after taking mifepristone, patients return for an additional clinical appointment within twenty-four to seventy-two hours before they could receive misoprostol to complete the treatment. A federal district court in South Dakota invalidated the state regulation as failing rational basis review.[290] Despite the fact that South Dakota cited studies from Australia and Finland in support of its position, the court decided the rule lacked a legitimate purpose because the FDA has "never required" that misoprostol be dispensed in a clinic.[291] "[I]f the [state's] Rule were concerned with patient health," said the court, "it would recommend that misoprostol be administered 24 to 48 hours after mifepristone, *as the FDA recommends*, and not 24 to 72 hours later as the Rule requires."[292] Here, the court used rational basis review to require that states not subvert the FDA's scientific expertise on medication abortion. For the same reason, under our agency reference model, such a regulation would likely be preempted.

Restrictions imposed by North Carolina present a more difficult line-drawing exercise. The state has enacted restrictions on the distribution and prescription of abortion-inducing drugs, including requirements that only physicians can do so. The physician must examine the patient in-person, determine the patient's blood type, and schedule a follow-up appointment within seven to fourteen days of administering the drug, among other restrictions.[293] Our model suggests that these restrictions should be preempted—especially if the FDA agrees and presents corroborating evidence—given that they undermine the FDA's risk-benefit analysis.

A federal district court in North Carolina validated our model in part. The court held that some of the state's restrictions, including the requirement that only physicians can prescribe mifepristone, and that the drug must be dispensed in person, were preempted because they were "designed to reduce the risks associated with the drug even though the FDA

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prescribed via telemedicine."). The court also noted that the state had encroached on the FDA's regulatory terrain. *See id.* (noting that, unlike the UCPA, the telemedicine regulation was not "upstream" from the mifepristone REMS—i.e., that the telemedicine regulation encroaches on the federal regulatory sphere whereas the UCPA sits squarely in the state regulatory sphere).

290. *See* Planned Parenthood Minn., N.D., S.D. v. Noem, 584 F. Supp. 3d 759, 783 (D.S.D. 2022), *appeal dismissed*, No. 22-1362, 2022 WL 3449758 (8th Cir. July 22, 2022). Although it did not decide the issue on preemption grounds, the court's reasoning aligns with our proposed framework.

291. *Id.* at 768–69.

292. *Id.* at 783 (emphasis added).

293. *See* N.C. GEN. STAT. § 90-21.83B (2023). Likewise, in Mississippi, only physicians can prescribe abortion pills; the physician must physically examine the recipient of the pills when doing so; and the physician must schedule a follow-up appointment within 14 days of administering the pills. MISS. CODE ANN. § 41-41-107 (2024).

explicitly considered and rejected that restriction as unnecessary for safe use under the statutory imposed and required by Congress."[294]

But the court deviated from our model by prizing legislative intent (and deference to state police powers) over the FDA's risk-benefit analysis in deciding that other restrictions, including in-person advance consultation, ultrasound, and in-person examination requirements, were *not* preempted because they address "broader health issues associated with pregnancy . . . about which the states remain free to regulate."[295] At this juncture, the court veered off course, embracing a dual sovereignty approach that deferred to the state on "broader health issues related to medical care or the information patients should have before deciding to terminate a pregnancy."[296]

Our agency reference model places the FDA, not the state legislature, at the center of courts' preemption analysis so as to anchor it in the agency's congressionally mandated risk calculus. Thus, given that the FDA had removed the in-person examination requirement (just as it had the in-person dispensing requirement), the state's requirement upends the FDA's risk-benefit analysis and should be preempted.

North Carolina's imposition of the ultrasound requirement—which the FDA considered but did not impose[297]—presents a thornier issue. For it is consistent with both the FDA's own position and the states' concurrent jurisdiction over the practice of medicine that states can enact regulations that are stricter than what REMS requires *in a complementary fashion*. Indeed, the FDA contemplates certain complementary state regulations. With regard to the special certification requirements for healthcare providers under the mifepristone REMS, the FDA states that "[s]ome states allow health care providers other than physicians to prescribe medications. Health care providers should check their individual state laws."[298]

A court may need to solicit input from the FDA in order to resolve whether a particular restriction is complementary, or at odds with, the

294. Bryant v. Stein, No. 1:23-CV-77, 2024 WL 1886907, at *15 (M.D.N.C. Apr. 30, 2024); *see also* Defendant Attorney General Joshua H. Stein's Memorandum of Law in Opposition to Intervenor-Defendants' Amended Motion to Dismiss at 21, Bryant v. Stein, No. 1:23-CV-00077 (M.D.N.C. Apr. 30, 2024) (ECF No. 86) (arguing that the laws "directly contradict the reasoned balance that the FDA – at Congress's discretion – has reached. Specifically, the laws impose restrictions that the FDA included in the mifepristone REMS, but ultimately rescinded, based on [its] considered judgment" about the risks).

295. *Bryant*, 2024 WL 1886907, at *12.

296. *Id.* at *14.

297. *Id.*

298. *See Questions and Answers on Mifepristone*, *supra* note 1.

REMS.[299] Returning to the ultrasound example, it is true that the FDA left the issue to the medical judgment of providers when it first approved mifepristone.[300] However, it is unclear how the agency's subsequent nixing of the in-person dispensing requirement would impact that assessment. Likewise, consider the Missouri law that, in addition to requiring a physical examination and follow-up visit, also mandates that physicians seek a state-approved "complication plan" before prescribing a drug "for the purpose of inducing an abortion" whose FDA label "includes any clinical study in which more than one percent of those administered the drug or chemical required surgical intervention after its administration."[301] This is clearly aimed at Mifeprex (the brand name of mifepristone), whose FDA-approved label says that, "[b]ecause heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with [certain blood disorders]."[302] The evidence on which Missouri's law relies is known to the FDA, which did not impose a "complication plan" requirement through the mifepristone REMS. But it would be exceedingly difficult for courts to determine whether this complication plan upsets the FDA's risk analysis without seeking input from the agency.

B. The Model's Limits: General Abortion Bans

We recognize that our proposed model to reconcile conflicts between FDA approval and REMS and state medication abortion restrictions has limits. We do not argue that the FDA's approval of mifepristone preempts general state bans on abortion. That said, if a state specified that its general abortion ban applies to FDA-approved drugs, the case for applying our model is strengthened. Here, we contrast the bans enacted in West Virginia and South Dakota, respectively.

West Virginia enacted the Unborn Child Protection Act (UCPA), which prohibits abortion in almost all cases,[303] and amounts to an effective (though

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299. It could do this by, for example, requesting the FDA's view on the issue or soliciting the FDA's intervention as amicus curiae. *See* Sharkey, *Products Liability Preemption*, *supra* note 13, at 504–06; Sharkey, *supra* note 164, at 1621–24; Catherine M. Sharkey, *The Opioid Litigation: The FDA is MIA*, 124 DICK. L. REV. 669, 690–91 (2020) [hereinafter *The Opioid Litigation*]; *see also supra* notes 142–45 & 259 and accompanying text.

300. *Bryant*, 2024 WL 1886907, at *14.

301. MO. REV. STAT. § 188.021(1)–(2) (2017).

302. *See* FDA, 3909592, MIFEPREX (MIFEPRISTONE) TABLETS LABEL (2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf [https://perma.cc/HM3A-5KHP].

303. *See* W. VA. CODE §§ 16-2R-1 to -9 (2022); *id.* § 61-2-8. It states that "[a]n abortion may not be performed or induced or be attempted to be performed or induced unless in the reasonable medical judgment of a licensed medical professional: (1) The embryo or fetus is nonviable; (2) The pregnancy is ectopic; or (3) A medical emergency exists." *Id.* § 16-2R-3(a).

not explicit) ban on mifepristone. The distinction between a ban on abortion *writ large* and mifepristone in particular is key to our preemption framework. When generic mifepristone manufacturer GenBioPro challenged the law on preemption grounds, the federal district court held that the state ban did not conflict with the FDA's actions on mifepristone because "West Virginia creates pre-requisites to accessing abortion care, while the REMS delineate logistical safety standards once a patient has sought medication abortion."[304] Given the court's view that the state's prerogative to ban abortion "coheres with traditional conceptions of the practice of medicine and the scope of physicians' authority as state matters," the court determined that the UCPA was a permissible "restriction on the incidence of abortion, rather than a state directive in direct conflict with the logistical REMS regulations."[305] In the parlance of our model, we agree with the court's conclusion because general abortion bans do not target the FDA's safety-and-effectiveness regulatory domain.

By contrast, South Dakota has expressly interpreted its general abortion ban to cover FDA-approved pharmaceuticals (namely mifepristone and misoprostol).[306] By taking this additional step, the state has opened itself up to a preemption challenge. By its own terms, South Dakota is not merely exercising its post-*Dobbs* prerogative to ban abortion. Rather, the state is expressly subverting the FDA's risk-benefit calculus with respect to these drugs, thereby intruding upon the FDA's safety-and-effectiveness decisional domain. According to our agency reference model, restrictions that target FDA-approved drugs can only withstand preemption if they *complement* the FDA's risk-benefit calculus. These clearly do not.

C. Beyond the Model: No FDA to Follow

A corollary of our model is that states have far greater leeway when regulating what the FDA has not considered. Focused as it is on drug safety and effectiveness, the agency cannot consider all potential consequences of

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304. GenBioPro, Inc. v. Sorsaia, No. 3:23-0058, 2023 WL 5490179, at *8 n.12 (S.D.W. Va. Aug. 24, 2023).

305. *Id.* at *8. Furthermore, it held that "GenBioPro is not regulated by the UCPA *at all*" because the law applies only to licensed medical professionals, and GenBioPro is not one. *Id.* As such, it did not need to decide whether the conduct prohibited by the UCPA "could include GenBioPro's sale of mifepristone to doctors and pharmacies" which it conceded was "debatable." *Id.*

306. *See* S.D. CODIFIED LAWS § 22-17-5.1 (2024) (prohibiting abortion except to save the life of the pregnant patient); State of S.D. Off. of the Governor, Open Letter Re: Enforcement Against Chemical Abortions by Retail Pharmacies (Jan. 24, 2023), https://governor.sd.gov/doc/GovNoem_AGJackley_Letter-to-Pharmacists.pdf [https://perma.cc/6RH3-AB5N] ("[S]ide-stepping on the part of the FDA permits dangerous, at-home abortions without any medical oversight. It also violates state law that makes dispensing this medication for abortions a felony.").

approving a drug. States can regulate what is orthogonal to the FDA's safety-and-effectiveness determination, such as drug compounding and matters of public health. Furthermore, there are several reasons why the FDA might not have evaluated the safety and effectiveness of a drug that is being administered off-label. Given the legality of off-label prescribing, a drug manufacturer may not have a commercial incentive to invest in the research necessary to secure supplemental NDA approval for an off-label use. Alternatively, it could be that the agency is in the midst of evaluating a drug for a new intended purpose and has not yet reached an approval decision. Various legal and political factors may also prevent the FDA from evaluating a drug's safety and effectiveness. In some of these situations, state regulatory action could generate benefits for drug safety and public health. But we fear state action also could lead to the imposition of restrictions based on low-quality scientific evidence, as we have seen in the realm of bans of gender-affirming care. Here, beyond our preemption model's reach, the need for the FDA's guidance is thrown into sharp relief.

States can regulate—either ex ante or ex post—the effects of an FDA-approved drug that are independent of the uses for which the agency has approved it. Beginning with ex ante, the FDA does not regulate compounded drugs.[307] Pharmacy-compounded drug mixtures can be dangerous, such as when one caused an outbreak of fungal meningitis in 2012.[308] Despite action by Congress to shore up the FDA's regulatory authority after this outbreak, pharmacies and large-scale compounding facilities alike are exempt from the labeling and premarket approval requirements for new drugs.[309] Here, state pharmacy boards can step in and regulate.[310]

As for ex post, the states can take measures to mitigate the effects of FDA-approved drugs on public health. For example, the FDA has been

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307. *See Compounding Laws and Policies*, FDA (Sept. 10, 2020), https://www.fda.gov/drugs/human-drug-compounding/compounding-laws-and-policies [https://perma.cc/RZ3B-82GS] ("Compounded drugs are not FDA-approved. This means that FDA does not review these drugs to evaluate their safety, effectiveness, or quality before they reach patients.").

308. *See id.*

309. *See* Rebecca S. Eisenberg & Deborah B. Leiderman, *Cannabis for Medical Use: FDA and DEA Regulation in the Hall of Mirrors*, 74 FOOD & DRUG L.J. 246, 270–71, 271 n.176 (2019) (citing 21 U.S.C. §§ 353a(a), 353b(a) (2019)).

310. *See Frequently Asked Questions About Pharmaceutical Compounding*, AM. PHARMACISTS ASS'N, https://www.pharmacist.com/Practice/Patient-Care-Services/Compounding/Compounding-FAQs#:~:text=The%20practice%20of%20compounding%20is,regulations%20outlined%20in%20Section%20503A [https://perma.cc/ZRE2-P8P2] (noting that state pharmacy boards and the Drug Enforcement Agency both regulate this area).

criticized for its role in the opioid crisis.[311] But in an important sense, the FDA approval process is not aimed at anticipating this kind of large-scale public health crisis.[312] The agency determines whether and under what conditions a drug is safe and effective for its intended use. It is beyond the FDA's capacity to anticipate the entire range of collateral consequences of its approval of a drug. In these circumstances, other federal agencies or the states can step in to regulate these externalities. For example, public awareness campaigns, like those carried out by the Centers for Disease Control and Prevention (CDC)[313] and the states[314] regarding opioid abuse, can help regulate the effects of an FDA-approved drug, without encroaching upon or undermining the FDA's safety-and-effectiveness domain.

The states must strike a delicate balance here, on pain of preemption. Above we advocated a presumption that regulations of FDA-approved drugs *are* regulations of drug safety and effectiveness.[315] So, to take the opioid example, state restrictions on the prescription and distribution of opioid analgesics must complement the applicable REMS.[316] The presumption does not apply, however, to generally applicable regulations that target *the effects* of FDA-approved drugs on the community as a whole.

As for FDA inaction, a mix of legal and political factors can influence whether the FDA has evaluated a particular drug's safety-and-effectiveness profile. Consider, for example, therapeutic uses of a federally illegal drug. Professor Eisenberg has argued that federal cannabis restrictions paradoxically lead to lower-quality data about these products, which are legal in some states.[317] Absent the incentive structure that the FDA approval

311. *See* Lars Noah, *Federal Regulatory Responses to the Prescription Opioid Crisis: Too Little, Too Late?*, 2019 UTAH L. REV. 757, 766, 773, 778–79 (arguing that the FDA should do more to regulate opioids); Sharkey, *The Opioid Litigation*, *supra* note 299, at 670–71 (proposing a preemption framework for courts that would "ensure that the [FDA] does not remain on the sidelines" and force the FDA to "acknowledge[] the role it has and will continue to play in the opioid epidemic"); *see generally* PATRICK RADDEN KEEFE, EMPIRE OF PAIN: THE SECRET HISTORY OF THE SACKLER DYNASTY 222, 225, 361 (2021) (describing how the FDA-approved painkiller OxyContin contributes to the opioid crisis).

312. *See* Patricia J. Zettler, Margaret Foster Riley & Aaron S. Kesselheim, *Implementing a Public Health Perspective in FDA Drug Regulation*, 73 FOOD & DRUG L.J. 221, 222–24 (2018) (arguing that the FDA's drug approval process is drug-specific—that is, narrowly focused on the benefits and risks of the drug in the context of its FDA-approved indication—and consequently does not focus on a drug's "real-world use and public-health impact").

313. *See Rx Awareness: About the Campaign*, CDC (Oct. 13, 2020), https://www.cdc.gov/rxawareness/about/index.html [https://perma.cc/47L2-XCMC].

314. *See* Jenna Frkovich, Haley Hedrick, Amarachi R. Anakaraonye, Alexandra Bornkessel & R. Craig Lefebvre, *Opioid-Related Public Health Communication Campaigns: An Environmental Scan*, 36 AM. J. HEALTH PROMOTION 913 (2022).

315. *See supra* Section III.C.1.

316. *See Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)*, FDA (Nov. 14, 2023), https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems [https://perma.cc/2G3K-9GQ7].

317. *See* Eisenberg & Leiderman, *supra* note 309, at 250.

process creates, alternative regulatory structures *can* incentivize the generation of some clinical data. Indeed, the legalization of medical marijuana in some states "provides an opportunity for collecting observational data without awaiting FDA approval of a [New Drug Application]."[318] But these data are second-best compared to the high-quality clinical data that the FDA's approval process typically generates.[319]

Yet another manifestation—and the most troubling one for our model—is when, for whatever reason, no sponsor has submitted the drug for FDA approval for a particular use. Consider the lack of an FDA-approved treatment for gender-affirming care.[320] Medical providers have been routinely prescribing certain drugs to transgender youths off-label for gender-affirming purposes.[321] Such off-label prescription of drugs falls within the purview of the "practice of medicine," regulated by the states.[322] In one sense, there is no need for an FDA-approved treatment if off-label ones are available. But, as twenty-five states have banned or severely restricted gender-affirming care for minors—including both surgical procedures and the prescription of drugs[323]—the lack of an FDA-approved treatment has taken on greater importance.

In the void of FDA inaction, several states have taken it upon themselves to regulate the safety and effectiveness of hormone therapies, which they assert are not safe for the purpose for which providers are prescribing them.

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318. *See id.* at 276–77.

319. *See id.* at 250–51.

320. *See* Chad Terhune, Robin Respaut & Michelle Conlin, *As More Transgender Children Seek Medical Care, Families Confront Many Unknowns*, REUTERS (Oct. 6, 2022, 11:00 AM), https://www.reuters.com/investigates/special-report/usa-transyouth-care [https://perma.cc/V96B-SLZP] (noting that puberty blockers and sex hormones are not FDA-approved for gender-affirming care, and that no clinical trials have established their safety or long-term effects for this use). Gender dysphoria refers to a condition of psychological distress that some transgender people may experience due to the incongruence between their gender identity and their sex assigned at birth. The term "gender-affirming care" refers more broadly to the range of social, psychological, behavioral, and medical interventions to affirm an individual's gender identity. *See* Patrick Boyle, *What Is Gender-Affirming Care? Your Questions Answered*, AAMC (Apr. 12, 2022), https://www.aamc.org/news/what-gender-affirming-care-your-questions-answered#:~:text=Gender%2Daffirming%20care%2C%20as%20defined,they%20were%20assigned%20at%20birth [https://perma.cc/B38Z-FVU9]. Gender-affirming care need not be administered to treat gender dysphoria.

321. Terhune, Respaut & Conlin, *supra* note 320 ("In a 2018 study published in the medical journal Clinical Pediatrics, researchers at Yale University noted a sharp increase in the off-label use of puberty blockers and said these drugs 'have not been thoroughly investigated in populations with normally timed puberty.'").

322. *See* United States v. Caronia, 703 F.3d 149, 153 (2d Cir. 2012) (citing Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001) (calling off-label use an "accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine")).

323. *See Map: Attacks on Gender Affirming Care by State*, HUM. RTS. CAMPAIGN (May 2024), https://www.hrc.org/resources/attacks-on-gender-affirming-care-by-state-map [https://perma.cc/4RSC-VJJV].

Thus, in response to a challenge brought to Oklahoma's ban,[324] the state focused attention on the potential safety risks associated with gender-affirming care. First, the state highlighted that the FDA has not approved puberty suppressors for gender-affirming uses.[325] Likewise, the state argued, testosterone "is not FDA-approved for gender transitions."[326] Finally, Oklahoma insisted that there is "a fierce dispute in the medical community as to whether any benefits from puberty blockers, hormones, and surgeries on minors exist at all, and whether they outweigh the many risks. And the State is entitled to take sides in that dispute."[327] Ultimately, a federal district court in Oklahoma agreed.[328]

Other judicial decisions rejecting challenges to states' gender-affirming care bans have explicitly relied on the absence of FDA approval of these treatments. Thus, the Sixth Circuit upheld bans enacted by Kentucky[329] and Tennessee[330] because, "[s]o long as a federal statute does not stand in the way and so long as an enumerated constitutional guarantee does not apply, the States may regulate or ban medical technologies they deem unsafe."[331] The court reasoned that, since "the FDA is not prepared to put its credibility and testing protocols behind the use" of hormones to treat gender dysphoria, there is no consensus in the medical community.[332] That the parties had each cited the practices of European nations for conflicting evidentiary propositions only bolstered the court's view that this was an unanswered question that states could decide for themselves.[333]

If some drug application sponsors have not acted for fear of wading into a contentious political debate, others are now seeking FDA approval for the very same reasons, and consequently an FDA-approved drug for such purposes may be on the horizon. The Research Institute for Gender Therapeutics (RIGT), a group advocating for FDA approval of gender-

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324. *See* Poe v. Drummond, No. 23-CV-177, 2023 WL 6516449 (N.D. Okla. Oct. 5, 2023).

325. Defendants 15-53's Response to Plaintiffs' Motion for Preliminary Injunction at 6, Poe v. Drummond, No. 23-cv-00177 (N.D. Okla. Oct. 5, 2023).

326. *Id.* at 8–9.

327. *Id.* at 18 (citation omitted) (citing Gonzales v. Carhart, 550 U.S. 124, 163 (2007) ("The Court has given state and federal legislatures wide discretion to pass legislation in areas where there is medical and scientific uncertainty.")).

328. *See Poe*, 2023 WL 6516449, at *14–16 (concluding that the state's regulation of gender-affirming care treatments for minors is rationally related to its interest in protecting their wellbeing "while the democratic process resolves ongoing questions of safety and efficacy").

329. KY. REV. STAT. ANN. § 311.372 (West 2023).

330. TENN. CODE ANN. § 68-33-101 (2023).

331. L.W. *ex rel.* Williams v. Skrmetti, 83 F.4th 460, 474 (6th Cir. 2023), *cert. dismissed in part sub nom.* Doe v. Kentucky, 144 S. Ct. 389 (2023), *cert. granted sub nom.* United States v. Skrmetti, No. 23-477, 2024 WL 3089532 (U.S. June 24, 2024).

332. *Id.* at 478.

333. *See id.*

affirming treatment, recently submitted to the FDA a plan for a Phase III clinical trial for estradiol—a common form of estrogen—to treat "gender incongruence." The FDA has provided RIGT preliminary feedback regarding how best to design its study; RIGT anticipates the study will begin in 2025.[334] Here, we consider the implications of our preemption model to guide courts facing future challenges to state bans on gender-affirming care should the FDA approve such a drug.[335]

Under our agency reference framework, should the FDA act to approve such a drug treatment, state bans would be preempted as, in effect, an indirect challenge to the FDA's determination of safety and effectiveness. Moreover, especially critical in this realm is the extent to which our agency reference framework would harness the FDA's capacity to generate information. Given the centrality of health and safety considerations of hormones and puberty blockers for gender-affirming purposes, the FDA is the proper forum. In the absence of FDA activity, states have rushed in to fill the void. Without the high-quality clinical data that the FDA approval process generates,[336] states have relied on secondary sources (without independent scientific vetting) when enacting these bans. For instance, as part of Arkansas's ban, minors and their parents or guardians can only consent to gender-affirming care after receiving verbal and written notice "verbatim" from the statute, including a statement that "Sweden, Finland, and the United Kingdom have conducted systematic reviews of evidence and concluded that there is no evidence that the potential benefits of puberty blockers and cross-sex hormones for this purpose outweigh the known or

334. *See* Theresa Gaffney, *The Push to Get Estrogen FDA-Approved for Gender-Affirming Care*, STAT (Nov. 28, 2023), https://www.statnews.com/2023/11/28/fda-gender-affirming-care-estrogen-approval [https://perma.cc/9FSR-TKJT]. The implications of FDA approval have not escaped notice. *See* Katherine Ellen Foley & Lauren Gardner, *FDA Weighs in on Gender-Affirming Care Study*, POLITICO (Dec. 1, 2023, 12:00 PM), https://www.politico.com/newsletters/prescription-pulse/2023/12/01/fda-weighs-in-on-gender-affirming-care-study-00129496 [https://perma.cc/EQ9C-V56J] ("Twenty-two states have banned gender-affirming care for minors . . . . FDA approval for estradiol for gender incongruence would be a legal argument against those bans."); Maya Goldman, *How the FDA Could Boost Gender-Affirming Care*, AXIOS (Dec. 15, 2023), https://www.axios.com/2023/12/15/fda-transgender-hormone-therapy-gender-affirming-care [https://perma.cc/3AEX-Y8F3] ("FDA approval could set off a new round of legal challenges over access to the treatments.").

335. Our framework applies separate and apart from constitutional challenges, such as on Equal Protection grounds, to state bans on gender-affirming care for young people. Equal protection claims have been central to such challenges. *See Skrmetti*, 83 F.4th 460. And the U.S. Supreme Court is now poised to resolve them. *See* Petition for a Writ of Certiorari, United States v. Skrmetti, No. 23-477 (U.S. June 24, 2024) (describing the question presented as: "Whether Tennessee Senate Bill 1 (SB1), which prohibits all medical treatments intended to allow 'a minor to identify with, or live as, a purported identity inconsistent with the minor's sex' or to treat 'purported discomfort or distress from a discordance between the minor's sex and asserted identity,' Tenn. Code Ann. § 68-33-103(a)(1), violates the Equal Protection Clause of the Fourteenth Amendment.").

336. *See supra* Section III.D.2.

assumed risks."[337] In so doing, state legislatures have transformed into fora for evaluating the safety and effectiveness of off-label uses of these drugs. Moreover, courts upholding bans have (at least implicitly) given judicial imprimatur to states' ad hoc health-and-safety evaluations. The Sixth Circuit concluded, moreover, that states may ban an off-label use of an FDA-approved drug if they decide, as Kentucky and Tennessee did, that such use "presents unacceptable dangers."[338]

What is missing returns us to the significant policy-based justification for the agency reference model, namely harnessing the FDA's ability to generate significant health and safety information.[339] The determination of which drugs are safe and effective for gender-affirming purposes should be based on rigorous evidence of safety and effectiveness—which drug sponsors are incentivized to produce and submit for FDA review—not political or ideological considerations.[340] What drives drug sponsors like RIGT to seek FDA approval in the first place could be the economic gains realized by selling an FDA-approved drug, or the threat of state restrictions in the void of FDA-approved treatments. Regardless, when they do so, drug sponsors are incentivized to generate the kind of high-quality data that would not otherwise exist.

CONCLUSION

At the core of highly contentious legal challenges to state regulations and restrictions on abortion medication lies the integrity of the FDA's scientific

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337. ARK. CODE ANN. § 16-114-403(b) (2023).

338. *Skrmetti*, 83 F.4th at 478. The states appear to see themselves as standing in for the FDA absent an approved drug. Significantly, if the FDA approves a drug, the states will lose this justification. A state might respond by enacting a total ban on gender-affirming care; and, pursuant to our model, FDA approval of a drug for gender-affirming care purposes would not preempt such a ban. But there may be political constraints on states' taking such a measure, in part given the FDA's gold standard reputation. Such bans, moreover, can be challenged on constitutional grounds, as in *Skrmetti*. *See supra* note 335.

339. *See supra* Section III.D.2.

340. *Compare* Press Release, Jonathan Skrmetti, Tennessee Attorney General Responds to Sixth Circuit Court of Appeals Decision in *L.W. v. Skrmetti* (Sep. 28, 2023), https://www.tn.gov/content /dam/tn/attorneygeneral/documents/pr/2023/pr23-41.pdf [https://perma.cc/8PC5-G2XG] ("Tennessee's law that protects children from irreversible gender-related medical interventions remains in effect. . . . Decisions that are not clearly resolved by the Constitution should be resolved by the people through their elected representatives."), *with* Press Release, Lambda Legal, Lambda Legal and TLDEF Urge Fourth Circuit to Uphold Rulings Protecting Gender-Affirming Care for Transgender People in North Carolina and West Virginia (Sept. 21, 2023), https://lambdalegal.org/newsroom/us_20230921_ll -tldef-urge-fourth-circuit-to-uphold-rulings-protecting-gender-affirming-care [https://perma.cc/Z973 -6UGV] (maintaining that gender-affirming care is "evidence-based, safe, and effective . . . [d]ecades of scientific and medical research as well as clinical experience, overwhelmingly support our understanding that gender-affirming care significantly improves the overall health and wellbeing of transgender people").

expertise. The centrality of the FDA and its scientific judgments comes to light with this Article's two key moves. The first is to create a typology of direct and indirect challenges to the FDA; the second is to bring both under the purview of a novel agency reference model.

The FDA's approval of mifepristone, and subsequent restrictions that the agency imposed on the drug through REMS, are the subject of *direct* challenges that the FDA acted arbitrarily. We characterize restrictive state laws and/or bans of abortion medication as *indirect* challenges to both the FDA's approval of mifepristone and the REMS restrictions imposed on the drug. A key insight emerges: challenges to state positive laws that involve areas of concurrent state and federal authority call upon courts to engage in an analysis that closely resembles the analysis used in implied preemption cases.

Central to our agency reference model is recognition of the primacy of the role played by the FDA in ensuring the safety and effectiveness of drugs. The FDA leads and states must follow with complementary regulation. Our model promotes national regulatory uniformity for an issue that Congress has addressed, but—equally significantly—it harnesses the FDA's capacity to incentivize the generation of high-quality clinical data about drugs' safety and effectiveness.