No. 21-1517

In the United States Court of Appeals for the First Circuit

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION

HEATHER PERHAM, ET AL.,
Plaintiffs-Appellants,

v.

GLAXOSMITHKLINE LLC,
Defendant-Appellee,

SUN PHARMACEUTICAL INDUSTRIES LTD.; SANDOZ, INC.; PROVIDENCE HEALTH SYSTEM; NOVARTIS PHARMACEUTICALS CORP.; MCKESSON CORPORATION; DOES 1 THROUGH 100, INCLUSIVE, TEVA PHARMACEUTICAL USA; GLAXOSMITHKLINE HOLDINGS (AMERICAS) INC.,
Defendants.

On Appeal from the United States District Court
for the District of Massachusetts
Case No. 1:15-md-02657-FDS (The Hon. F. Dennis Saylor IV)

MOTION BY AMERICAN ASSOCIATION FOR JUSTICE AND PUBLIC JUSTICE FOR LEAVE TO FILE AMICUS CURIAE BRIEF IN SUPPORT OF PLAINTIFFS-APPELLANTS

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March 23, 2022

Proposed amici curiae the American Association for Justice ("AAJ") and Public Justice respectfully move this Court, pursuant to Federal Rule of Appellate Procedure 29(b), for leave to file the proposed amicus curiae brief in support of the plaintiffs-appellants. Both the plaintiffs and the defendants consent to this request. The brief is being filed within seven days of the plaintiffs-appellants' brief.

The plaintiffs ask this Court to reverse a district court decision immunizing drug manufacturers from state-law failure-to-warn claims regarding the risk of birth defects associated with the prescription drug Zofran. The attached amicus brief addresses one aspect of the district court's decision: whether either the Federal Drug Administration's disapproval of a different warning, or its silence when presented with evidence supporting the warning the plaintiffs seek, amounts to an agency action that carries preemptive force.

AAJ is a national, voluntary bar association established in 1946 to strengthen the civil justice system, preserve the right to trial by jury, and protect access to the courts for those who have been wrongfully injured. With members in the United States, Canada, and abroad, AAJ is the world's largest plaintiff trial bar. AAJ's members primarily represent plaintiffs in personal injury actions, employment rights cases, consumer cases, and other civil actions, including in state nursing home cases. Throughout its more than seventy-year history, AAJ has served as a leading advocate for the right of all Americans to seek legal recourse for wrongful conduct.

Public Justice is a national public interest advocacy organization that specializes in precedent-setting, socially significant civil litigation, with a focus on fighting corporate and governmental misconduct. Public Justice has long maintained an Access to Justice Project, which seeks to ensure that the civil courts are an effective tool that people with less societal power can use to win just and equitable outcomes and hold to account those with more power. To that end, Public Justice has an interest in ensuring that federal preemption law is not used to deny victims of corporate misconduct access to justice. Public Justice works to ensure that courts apply the proper standard for federal preemption, so that the doctrine does not become a shield for corporate wrongdoing and that consumers, including those harmed by dangerous products with inadequate warnings, can seek legal recourse.

Proposed amici are well-positioned to assist the Court with the issues at stake in this case because amici and their members have experience in pharmaceutical-related failure-to-warn litigation. As explained in the brief, the expansion of federal preemption the defendants urge is both contrary to precedent and practically pernicious.

Proposed amici respectfully request that the Court grant them leave to file the attached amicus curiae brief.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on March 23, 2022, I electronically filed the foregoing motion and amicus brief with the Clerk of the Court for the U.S. Court of Appeals for the First Circuit by using the CM/ECF system. All participants are registered CM/ECF users, and will be served by the appellate CM/ECF system.

/s/ Matthew W.H. Wessler
Matthew W.H. Wessler

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BRIEF OF AMICI CURIAE AMERICAN ASSOCIATION FOR JUSTICE AND PUBLIC JUSTICE IN SUPPORT OF PLAINTIFFS-APPELLANTS

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Regulations

Constitutional Provisions

INTEREST OF AMICUS CURIAE[1]

The American Association for Justice ("AAJ") is a national, voluntary bar association established in 1946 to strengthen the civil justice system, preserve the right to trial by jury, and protect access to the courts for those who have been wrongfully injured. AAJ's members primarily represent plaintiffs in personal injury actions, employment rights cases, consumer cases, and other civil actions. Throughout its 75-year history, AAJ has served as a leading advocate for the right of all Americans to seek legal recourse for wrongful conduct.

As this brief explains, in the years since *Wyeth v. Levine*, 555 U.S. 555 (2009), drug manufacturers have attempted to curtail consumers' state-law rights by arguing for an expansive theory of conflict preemption that would preempt failure-to-warn state laws based on only hypothetical conflicts with federal law. These attempts have continued even after the Supreme Court's recent decision reaffirming *Wyeth* in *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019). Based on its members' experience with pharmaceutical tort litigation—and its organizational concern for the development of the law in this area—AAJ is well-positioned to explain why the expansion of federal preemption the defendants urge in this case is both ill-conceived and contrary to precedent.

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[1] No counsel for any party authored this brief in whole or in part. Apart from the amici curiae, no person, party, or party's counsel contributed money intended to fund the brief's preparation and submission.

Public Justice is a national public interest advocacy organization that specializes in precedent-setting, socially significant civil litigation, with a focus on fighting corporate and governmental misconduct. Public Justice has long maintained an Access to Justice Project, which seeks to ensure that the civil courts are an effective tool to win just and equitable outcomes. To that end, Public Justice has an interest in ensuring that federal preemption law is not used to deny victims of corporate misconduct access to justice. Public Justice works to ensure that courts apply the proper standard for federal preemption, so that the doctrine does not become a shield for corporate wrongdoing and that consumers—including those harmed by dangerous, inadequately labeled products—can seek legal recourse.

INTRODUCTION AND SUMMARY OF ARGUMENT

The Food, Drug, and Cosmetic Act was enacted "to bolster consumer protection against harmful products." *Wyeth*, 555 U.S. at 574. When Congress enacted this expansive consumer protection statute, however, it didn't create a right of action for consumers harmed by unsafe or ineffective drugs—it didn't need to, because state law already supplied one. *See id.* at 574 & n.7. Indeed, "[c]ourts entertained tort litigation against [drug] manufacturers since well before the passage" of the FDCA, and such litigation has long been a "common feature of the legal landscape." *Bates v. Dow AgroSciences LLC*, 544 U.S. 431, 440–41 (2005); *see also*

Wyeth, 555 U.S. at 575 (finding "powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness").

Because of the historic role state tort law plays in regulating health and safety, the Supreme Court has reiterated time and again that implied impossibility preemption—the displacement of state tort law by federal regulatory law—is a "demanding defense." *Wyeth*, 555 U.S. 573. In *Wyeth*, the Court established the cornerstone principle that impossibility preemption does not foreclose state-law failure-to-warn claims simply because a federal agency regulates product labeling. Instead, the relevant question when a manufacturer attempts to raise the shield of preemption is whether federal law would have permitted the manufacturer to alter its label to comply with the state law obligation, or whether the federal agency actually would have rejected that change. *See id.* at 568–73. And, the Court held, only "clear evidence" that complying with the state law obligation would force a violation of federal law can justify knocking out a state law claim.

A decade later, in *Albrecht*, the Court reaffirmed this exacting standard and provided further guidance on what constitutes "clear evidence." 139 S. Ct. 1668, 1679 (2019). "[C]lear evidence," the Court explained, is "evidence that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to

include that warning." *Id.* at 1672. Thus, a court considering an impossibility preemption defense must ask "whether the relevant federal and state laws irreconcilably conflict." *Id.* at 1679.[2] And, the Court noted that the only agency actions that can determine the answer to preemption questions are those "taken pursuant to the FDA's congressionally delegated authority." *Id.*

Despite these lessons, drug manufacturers have vigorously pursued an approach to impossibility preemption that does not turn on whether state and federal law "irreconcilably conflict." *Id.* Instead, their approach encourages courts to engage in a speculative, freewheeling judicial inquiry into whether compliance with state law would *potentially* violate federal law—the kind of "hypothetical or potential conflict" that *Wyeth* and *Merck* decisively rejected.

That is precisely what happened here. The defendants' preemption defense rests on mere speculation that the FDA *would* have rescinded a warning that the manufacturers never actually proposed. They base this speculation on the agency's rejection of a different warning, based on different scientific data, that merely concerned the same category of risk—adverse effects during pregnancy. Based on this, the district court concluded that it would have been "impossible" for the manufacturers to add the warnings that the plaintiffs seek—even when the record

[2] Unless otherwise specified, internal quotation marks, citations, emphases, and alterations are omitted from quotations throughout the brief.

shows the FDA did not consider whether the evidence supported the plaintiffs' warning, much less "inform[]" the manufacturer it would not approve such a warning. *Albrecht*, 139 S. Ct. at 1672.

This view of impossibility preemption contravenes Supreme Court preemption doctrine in at least three ways. For starters, it runs headlong into *Wyeth* and *Albrecht*, two cases in which the Supreme Court rejected the argument advanced here—that the FDA's disapproval of a different warning concerning the same kind of risk has any preemptive effect. It also ignores the practical reality that the FDA might reject a warning for any number of reasons—including many that would carry no preemptive consequences for a state-law failure-to-warn claim. And finally, the district court's reasoning cannot be squared with the established principle that agency *in*action has no automatic preemptive effect. The FDA's silence—the fact that it did not on its own require the manufacturer to add the warning the plaintiffs seek—is simply not the kind of "action" that carries the force of law sufficient to displace state law. *See Sprietsma v. Mercury Marine*, 537 U.S. 51, 65 (2002).

To uphold the district court's contrary view would create an end-run around the "demanding defense" of impossibility preemption and erode critical state-law protections that Congress intended would ensure drug safety and effectiveness. This Court should reverse.

ARGUMENT

I. A state-law failure-to-warn claim is only preempted on impossibility grounds if the FDA actually rejected the specific warning that the plaintiff's lawsuit would have required.

It has been settled for at least forty years that there can be no conflict preemption with federal law if there is only "a hypothetical or potential conflict" between state and federal law. *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982). Instead, where conflict preemption is alleged, state law is only preempted "to the extent that it *actually* conflicts with federal law." *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990) (emphasis added). As a result, when a party asserts that its state-law obligations were preempted because it was impossible to comply with both state and federal law, the party must demonstrate that it was actually "not lawful under federal law . . . to do what state law required." *PLIVA, Inc. v. Mensing*, 564 U. S. 604, 618 (2011).

This demanding rule is rooted in the Supremacy Clause of our federalist system. Under the Supremacy Clause, state law is preempted only by federal law "made in Pursuance" of the Constitution—not by extratextual considerations that may require speculation or hypothesis. U.S. Const., art. VI, cl. 2. Because the States are independent sovereigns in our federal system, the Supreme Court has "long presumed that Congress does not cavalierly pre-empt state-law causes of action." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996). Thus, when Congress legislates in "a

field which the States have traditionally occupied," courts must "start with the assumption that the historic police powers of the States were not to be superseded by [federal law] unless that was the clear and manifest purpose of Congress." *Id.* This approach is consistent with both federalism and the historic primacy of state regulation over matters of health and safety.

It is for this reason that a preemption analysis "should not be [a] freewheeling judicial inquiry into whether a state statute is in tension with federal objectives, but an inquiry into whether the ordinary meanings of state and federal law conflict.'" *Wyeth*, 555 U.S. at 588 (Thomas, J., concurring). In other words, impossibility preemption takes places only "where it is impossible for a private party to comply with both state and federal requirements." *Mensing*, 564 U.S. at 618. *See also Hillsborough Cnty. v. Automated Med. Lab'ys*, 471 U.S. 707, 718 (1985) (holding that courts must assume "that state and local regulation . . . can normally coexist with federal regulations").

A. Drug manufacturers have repeatedly sought to water down *Wyeth*'s instruction that impossibility preemption requires a "demanding" showing.

The Supreme Court's landmark decision in *Wyeth* sets out the governing framework whenever a drug manufacturer presses an impossibility preemption theory of implied preemption. In that case, Diane Levine received two doses of Phenergan, an anti-nausea drug manufactured by Wyeth to treat nausea caused by

migraine headaches. *Wyeth*, 555 U.S. at 558–59. Phenergan can be administered via the "IV-push" method, where the drug is injected directly into a patient's vein, or the "IV-drip" method, where the drug is presented in a saline solution in an intravenous bag and slowly enters a patient's vein through a catheter. *Id.* The drug is known to cause irreversible gangrene if it enters an artery. *Id.* at 559. After an IV-drip dose of Phenergan failed to relieve Levine's nausea, a second dose was administered via the riskier IV-push method, which entered Levine's artery, caused gangrene, and eventually resulted in the amputation of her forearm. Levine sued Wyeth for failing to include a warning regarding the risk of gangrene from the IV-push method, but Wyeth claimed that it could not have adopted that warning because federal regulations prevented it from changing the drug's label. *Id.* at 559, 563–64.

The Supreme Court rejected that argument, holding that Levine's failure-to-warn claim was not preempted. *Id.* at 570–71. The Court noted that the FDA's "changes being effected" regulation permits drug manufacturers to add new warnings to their labels, which meant that Wyeth "could have . . . added a stronger warning." *Id.* at 568, 570. And the Court recognized that it is the manufacturer's primary responsibility—not an agency's—to ensure its label is accurate and its product is safe. *Id.* at 568–73. While the FDA could act to reject those changes, the Court explained that the mere possibility that an agency *might* reject a label change

was not enough to trigger impossibility preemption. *Id.* at 571. Instead, the Court held that impossibility preemption in a failure-to-warn case is not a valid defense unless there was "clear evidence" that the agency "would not have approved [the] change" in question. *Id.*

In the years after *Wyeth*, however, drug manufacturers used this "clear evidence" standard to pursue a theory of preemption that did not turn on actual impossibility—whether the manufacturer could have added a particular warning to its label—but rather on hypothetical impossibility—whether the manufacturer could not have included the warning because the FDA *would have* rejected it. *See, e.g.*, *Forst v. Smithkline Beecham Corp.*, 639 F. Supp. 2d 948 (E.D. Wis. 2009); *Dorsett v. Sandoz, Inc.*, 699 F. Supp. 2d 1142 (C.D. Cal. 2010); *Lofton v. McNeil Consumer & Specialty Pharms.*, 682 F. Supp. 2d 662 (N.D. Tex. 2010); *Hunt v. McNeil Consumer Healthcare*, 6 F. Supp. 3d 694 (E.D. La. 2014); *Koho v. Forest Lab'ys*, 17 F. Supp. 3d 1109 (W.D. Wash. 2014).

Several of these cases show just how far manufacturers have attempted to push this theory of impossibility preemption. In *Forst*, for example, a manufacturer claimed the FDA's "repeated review" of a drug's safety issues and the "amount of interaction" it had with the agency amounted to "clear evidence" that the FDA actually concluded the plaintiffs' warnings were "unwarranted and inappropriate." *Forst*, 639 F. Supp. 2d at 954. In *Crockett v. Luitpold Pharmaceuticals*, a manufacturer pointed to two FDA pre-approval letters that just cited the relevant risk as "'evidence'

that [the manufacturer] proposed a stronger warning to the FDA [and] that the FDA would have rejected a different warning label." 2020 WL 433367, at *7 (E.D. Pa. Jan. 28, 2020). And in *Hunt*, a manufacturer claimed that a letter from the FDA ordering manufacturers to supplement existing warnings about one drug somehow proved that the manufacturer could not have added stricter warnings about a different drug. 6 F. Supp. 3d at 701. As these cases illustrate, the theory of impossibility preemption advanced by some manufacturers turns not on whether it would have been impossible to comply with both state and federal law, but on theoretical assumptions and extratextual clues about what the FDA would have done.

B. *Albrecht* shut the door on manufacturers' hypothetical preemption claims.

In *Albrecht*, the Supreme Court firmly rejected manufacturers' attempts to establish "clear evidence" based on conjecture.

The plaintiffs in *Albrecht* alleged that Fosamax, a drug intended to treat bone loss, caused them to suffer atypical femoral fractures, and Fosamax's FDA-approved label failed to adequately warn of the risk of these fractures. *Albrecht,* 139 S. Ct. at 1675. Merck argued that the plaintiffs' claim was preempted. Merck did not argue—because it could not—that the agency actually rejected a proposed label regarding atypical femoral fractures. So instead, the company argued that the plaintiffs' desired warning *would have been* rejected by the FDA because the agency previously rejected

Merck's attempt to warn of a risk of "stress fractures." *Id.* at 1674. Earlier, Merck had proposed adding to the label a discussion of "stress fractures," but the FDA rejected that warning, concluding that the company's "justification" for the change was "inadequate." *Id.*

To defend against the plaintiffs' state-law claims that Merck failed to warn of the risk of atypical femoral fractures, Merck relied on the FDA's rejection of different stress-fracture language as evidence that if the company *had* requested such a change, the FDA would have rejected it.

The Court decisively rejected this hypothetical-preemption argument. It reaffirmed that impossibility preemption turns on actual "agency disapproval." *Id.* at 1680–81. It is "not enough," the Court explained, for there to be a "possibility of impossibility." *Id.* at 1678. Rather, impossibility preemption exists only where federal law and state law "irreconcilably conflict," *id.* at 1679—where federal law *actually* "prohibit[s] the [] manufacturer from adding any and all warnings to the [] label that would satisfy state law," *id.* at 1678.

The Court also made clear that, regardless of the FDA's authority, it is *the manufacturer* that bears the "ultimate responsibility for its label." *Id.* at 1677. It therefore cannot avoid "state laws that would penalize [it] for failing to warn consumers of the risks" associated with its product without clearly showing that compliance would in fact force it to violate federal law. *Id.*

In this way, *Albrecht* provided straightforward guidance on how to perform the impossibility-preemption inquiry. Although the Court chose not to "further define *Wyeth*'s use of the words 'clear evidence' in terms of evidentiary standards," it made clear that the analysis is "tightly circumscribed." *Id.* at 1679–80. It identified the only type of evidence that could count: those "agency actions" taken pursuant to congressionally delegated authority. *Id.* at 1679. And the Court further defined those specific forms of agency action that, under relevant federal law, could trigger impossibility preemption—disapproval of a specific warning either (1) "by means of notice-and-comment rulemaking setting forth labeling standards," (2) "by formally rejecting a warning label that would have been adequate under state law," or (3) "with other agency action carrying the force of law." *Id.*

Finally, *Albrecht* established a clear, two-step framework for determining whether a manufacturer has met the "demanding defense" of impossibility preemption. *Id.* at 1672, 1678. First, a court must determine whether a manufacturer "fully informed" an agency of a product's risks. *Id.* at 1679. If it failed to do so, the inquiry stops and no impossibility preemption exists. *See id.* Second, if the agency was fully informed of a product's risks, the manufacturer must then show that the agency, acting within the scope of its lawful authority, "informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning."

Id. Both circumstances must be met in order for a court to conclude that state-law failure-to-warn claims are foreclosed.

In the wake of *Albrecht*, lower courts have begun to hold drug manufacturers to this demanding standard. In *In re Avandia Marketing, Sales and Products Liability Litigation*, for instance, a manufacturer claimed that it had "fully informed" the agency about a drug's safety risks because it "provided all 'material' information" to the agency, and the agency had actually "rejected the proposed warning." 945 F.3d 749, 756–58 (3d Cir. 2019). In support, the manufacturer pointed to a prior application that sought to add information that would make the drug's warning "more prominent and clear." *Id.* at 753. The FDA responded that the proposed change was "not approvable" because the information presented was "inadequate." *Id.*

The Third Circuit rejected the impossibility-preemption defense, holding that the manufacturer had "failed to satisfy either prong" of *Albrecht*'s two-step test. *Id.* at 758. First, the manufacturer had "not shown" that it fully informed the agency "of the justifications for the warning required by state law" because the agency itself had found the information "inadequate" and informed the manufacturer that it "needed to submit various data and information in order to address the deficiency." *Id.* And the court rejected the manufacturer's effort to show that the agency actually "rejected the proposed warning." *Id.* at 759–60. That was so, the court held, because

the agency's label rejection had nothing to do with "the need for a strong warning;" instead, it was "because the information presented" was "inadequate." *Id.* at 759. "At most," it was "possible" that the agency "could have rejected the label change after receiving the various data and information it requested." *Id.* at 760. But, the court reiterated, "the possibility of impossibility is not enough." *Id.* (quoting *Albrecht*, 139 S. Ct. at 1678).

II. The district court's ruling cannot be squared with the principles that govern impossibility preemption.

In this case, the plaintiffs argued that at the time of their injuries, Zofran should have carried a Pregnancy Category C label, "which would have informed physicians of the existence of animal data suggesting adverse fetal effects." Addendum 59. In the district court's view, this claim was preempted under *Wyeth*'s "clear evidence" standard. *Id.* at 62–63. But the district court reached this conclusion not because the FDA *actually* rejected a warning that would inform physicians about the existence of animal data suggesting adverse effects—the FDA never said anything about this data. *Id.* at 60. The court instead held that the standard had been met because the FDA had rejected different warnings—generalized safety pregnancy warnings related to human epidemiological studies—that concerned the same category of risk. *Id.* at 60–63. No understanding of the controlling principles of impossibility preemption permits such an approach.

A. The district court engaged in improper hypothetical preemption.

As the plaintiffs' opening brief explains (at 21–23), in 2020 the FDA rejected Novartis's proposal to add generalized pregnancy warnings to Zofran's label, including that "[t]he use of [Zofran] in pregnancy is not recommended." Addendum 25 (citing Hill Suppl. Decl., Ex. 197 at 6486). To support this proposed warning, Novartis told the FDA that it was based on "recently published [human] epidemiological studies with new data on the risks of birth defects." Addendum 22 (citing Hill Decl., Ex. 190 at 1). After a series of exchanges, the FDA rejected Novartis's proposed warning language, reasoning that "limitations in the design of [the epidemiological] studies," and "inconsistency in published epidemiology findings" meant that "the available data do not support a recommendation to avoid Zofran in pregnancy." Addendum 25 (citing Hill Decl., Ex. 197 at 6486).

Nothing about this agency action, however, concerned risk based on animal studies. All that the FDA did in rejecting Novartis's proposal was reject generalized warnings based on admittedly limited human epidemiological data. But this says nothing about whether the FDA would have rejected a *different* warning—based on different data—that the plaintiffs' lawsuit seeks. In other words, the agency never in fact "reject[ed] a warning label that would have been adequate under state law." *Albrecht*, 139 S. Ct. at 1679. Indeed, Novartis did not propose, and the agency did not reject, *any* changes to the Zofran label's "Risk Summary" section concerning

animal studies, or to the animal data subpart within the pregnancy section. *See* Notice by GSK of FDA's Labeling Revisions, April 29, 2021, Ex. A at Pub_11022; Addendum 60 (recognizing that "Novartis did not propose any changes to that language").

That meant the district court could only speculate about what the FDA *might have done* had it actually been presented with a proposed warning regarding the precise risks the plaintiffs say should have been included. *See* Addendum 59–61. This kind of freewheeling hypothetical speculation is wrong for at least three reasons. *First*, the FDA's rejection of one warning is not tantamount to the rejection of a different warning, just because both warnings fall within the same general category—adverse effects during pregnancy. If that were the rule, both *Wyeth* and *Albrecht* would have come out the other way. *Second*, the district court's reasoning ignores the fact that the FDA rejects proposed warning language for a multitude of reasons. It is therefore improper to speculate that the agency's rejection of one warning necessarily means that a different warning would also be rejected. And *third*, the court's impermissible view of impossibility preemption would reward drug manufacturers for subterfuge, inviting them to manipulate the federal regulatory process to escape the consequences of their own negligence.

1. The district court's basis for finding preemption here was its hypothesis that if Novartis *had* asked for a change to the animal studies subsection, the FDA would

have denied it because the agency denied other related and more generalized pregnancy warnings. In the court's view, if an FDA rejection of a proposed warning mentions the relevant risk, that is sufficient to establish that the FDA would have rejected *any* warning falling in the same risk category.

But under *Albrecht* and *Wyeth*, that type of speculation is foreclosed. In *Wyeth*, the manufacturer had proposed—years before the plaintiff's injury—"different language" for Phenergan's warning about the risk of an intra-arterial injection through the IV-push method. 555 U.S. at 572 n.5 (majority); *see also id.* at 605 n.1 (Alito, J., dissenting). And the FDA had even considered whether to prohibit a syringe system used exclusively for IV push, before ultimately agreeing to provide better instruction about the problem of intra-arterial injection. *Id.* at 613–17 (Alito J., dissenting); *see also Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392–93 (7th Cir. 2010) (discussing Phenargan's regulatory history). But, the Court held, even though the FDA had explicitly considered a similar warning to the one the plaintiff proposed, this had no preemptive effect on her state-law failure-to-warn claim. *Wyeth*, 555 U.S. at 572. Ultimately, the FDA had "paid no more than passing attention" to IV-push warnings, and it made no "affirmative decision" to either preserve that method or prohibit Wyeth from strengthening its warning about it. *Id.* As the Court made clear, regardless of these earlier proposals, it would not have been *impossible* for Wyeth to have added that sort of warning. *Id.*

The same goes for *Albrecht*. Just as in *Wyeth*, Merck argued that adding a warning about atypical femur fractures would have been impossible because the FDA had already rejected language that warned about that same category of risk—femoral fractures. *Albrecht*, 139 S. Ct. at 1675. The actual warning the FDA had considered and rejected discussed the risk of "stress fractures," which the FDA had concluded "may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." *Id.* at 1674. But as it did in *Wyeth*, the Supreme Court rejected the theory that the FDA's disapproval of a warning that mentioned the same type of risk amounts to "clear evidence" that the FDA would have actually rejected a different attempt to warn of that risk. *See id.* at 1678–79. Instead, the Court emphasized that a manufacturer must show the FDA actually "*informed* the drug manufacturer that the FDA would not approve changing the drug's label to include *that warning*." *Id.* at 1678 (emphasis added).

The district court's impossibility-preemption analysis here cannot be squared with these two controlling decisions. And the record in this case provides even less support for the contention that the FDA ever "gave more than passing attention" to the warnings the plaintiffs actually seek. *Wyeth*, 555 U.S. at 572. The FDA's back-and-forth with Novartis makes clear that the agency's attention was not directed toward the animal studies at all; it was trained appropriately on the sufficiency of the *human* epidemiological studies that should support the *actual* labeling changes

Novartis sought. *See, e,g.*, Addendum 25 (discussing Hill Suppl. Decl. Ex. 197 at 6485 (revising proposed labeling language about "human epidemiological studies")); *id.* (discussing "inconsistency" in "published epidemiology findings" concerning "maternal ondansetron use"); Addendum 27 (discussing Notice by GSK of FDA's Labeling Revisions, April 2, 2021, Ex. A, at 2027 (proposing revision to the human data section of label)).

The FDA's actual formal rejection—the only action that matters for preemption purposes—bears this out. Beyond a small grammatical change to add a clarifying word to the animal data section, *see* GSK's April 30, 2021 Notice of FDA's Approval of Updated Labeling, Exs. A–D, Pub_11019–11066, there is no evidence—much less "clear evidence"—that the agency paid more than "passing attention" to the question whether animal studies would support a stronger warning in the animal data subpart of Zofran's label. *Wyeth*, 555 U.S. at 572. Just as in *Wyeth* and *Albrecht*, this is not enough to meet the exacting burden of impossibility preemption.

2. The district court's approach to preemption also failed to appreciate the practical reality that the FDA rejects specific warning label proposals for all sorts of reasons—many of which carry no preemption consequences whatsoever.

The FDA might, for example, reject certain warning language because it contains various "deficiencies" about which the agency requires more information.

See In re Avandia, 945 F.3d at 759–60. But a court may not presume from that rejection that the FDA "was unconvinced of the need for a strong warning." *Id.* at 760. Or, the FDA might reject a proposed warning that mentions specific terms or conditions that would be unfamiliar to consumers. *See Reckis v. Johnson & Johnson*, 471 Mass. 272, 288–89 (2015). But that doesn't mean the agency would reject a warning about those same conditions phrased more generally. *See id.* (holding that a state-law warning claim that would have warned about "serious skin reactions" was not preempted, even though the FDA had earlier rejected proposal that would have named specific skin diseases).

Likewise, the FDA might reject a proposal to add a "black box" warning—the strongest type of warning allowed in drug labeling—but that doesn't mean the agency would reject a warning about that same risk were it placed elsewhere on the drug's label. *See In re Taxotere (Docetaxel) Prods. Liab. Litig.*, 508 F. Supp. 3d 71, 86 (E.D. La. 2020) (holding there was "no clear evidence" the FDA would have rejected a warning about permanent alopecia in the "Adverse Reactions" portion of a drug's label merely because the FDA had rejected a "black box" warning about that condition). *See also Risperdal & Invega Cases*, 49 Cal. App. 5th 942, 959–60 (2020)

("Hypothetical labeling changes and speculative future rejections are not clear evidence of an impossibility preemption defense.").[3]

Here, as explained above, the FDA rejected Novartis's generalized pregnancy warnings because it concluded that warning was not supported by the existing human epidemiological data. But that rejection says nothing about whether the agency would have permitted a different warning supported by different data. Even the FDA's own regulations recognize that risk statements based on human data and those based on animal data are different. *See* 21 CFR 201.57(c)(9)(i)(B)(1) & (2) (2015). A risk statement based on human data—the type of risk statement that Novartis requested—must be supported by "human data" that "establish[es] the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug." *Id.* at (c)(9)(i)(B)(1). A risk statement based on animal data, by contrast, relies on "findings in animals." *Id.* at (c)(9)(i)(B)(2). The agency's rejection of one risk statement, then, says nothing about whether a different risk statement would have also been rejected.

[3] For this reason, the FDA's rejection of GSK's citizen petition also fails to supply "clear evidence" of FDA disapproval. As the plaintiffs explain, *see* Pls. Br. at 54–55, the FDA rejected GSK's citizen petition not because it found the proposed warnings unwarranted, but because GSK's request was "not the appropriate subject of a citizen petition." *Id.* at 54 (citing Pub_010469). Indeed, the agency explicitly denied the request "without comment on the relevance, if any, of this information to [Zofran] product labeling," and therefore the denial exerts no preemptive force on the plaintiffs' claims. *Id.*

3. Finally, the district court's approach—authorizing preemption where the FDA rejects a different warning relevant to the same risk area—also risks creating what Justice Gorsuch has called "a moral hazard." Tr. Oral Argument at 13, *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019) (No. 17-290). Manufacturers would be incentivized "to supply the FDA with a lot of information"—some pointing one way, some pointing the other way—only to then ask the agency to approve "maybe not the most artfully drafted and maybe deliberately inartfully drafted warning." *Id.* Or, as here, the manufacturer could request a related but inadequately supported warning—one that the manufacturer "thinks is reasonably calculated to be refused, so that it can avoid having to shoulder or . . . internalize its own costs of negligence." *Id.* In other words, all a manufacturer would need to do to preempt a broad array of state-law claims is propose a generalized warning related to those claims that it anticipates would be rejected—perhaps because the language is inexact, or perhaps because the warning outstrips the data that should support it. Under the district court's view of impossibility preemption, the FDA's rejection of that unsupported warning would preempt any state-law claim seeking a different warning, so long as both warnings touch on the same relevant risk.

That is why there is simply no room in an impossibility-preemption inquiry to speculate why, perhaps, "federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would

satisfy" the plaintiffs' state law claims. *Albrecht*, 139 S. Ct. at 1678. Instead, the "tightly circumscribed" inquiry asks only whether federal law *actually* prohibited the drug manufacturer from including the particular warning sought by a failure-to-warn suit. *Id.* at 1680. The district court impermissibly strayed from the bounds of this analysis, engaging in exactly the kind of hypothetical-impossibility approach that the Supreme Court has rejected. As both *Wyeth* and *Albrecht* make clear, the preemptive power exerted by the FDA's rejection of a proposed warning goes only as far as the warning itself and the FDA's reason for rejecting it—beyond that is anyone's guess. The district court erred in holding otherwise.

B. The district court impermissibly held that agency silence could trigger impossibility preemption.

The district court's ruling also runs afoul of the established principle that agency silence cannot serve as a basis to preempt state-law claims. In reasoning that the FDA's rejection of Novartis's earlier proposed warning amounted to "clear evidence" under *Merck*, the district court said that, although the "FDA was [] pointed specifically to the very evidence that plaintiffs contend requires a label warning," it did not on its own propose a different warning based on that evidence. Addendum 60. It would be "highly unlikely," the district court speculated, that the agency "turned a blind eye" to this supposed evidence even though, as a "technical point," Novartis didn't seek any changes related to that evidence or to that part of the label. *Id.* at 61.

Once again, *Albrecht* forecloses this agency-silence theory of preemption. The Court in *Albrecht* held unequivocally that, to satisfy the "clear evidence" standard and thus trigger impossibility preemption, a drug manufacture must show first that "it fully informed the FDA of the justifications for the warning," and second, "that the FDA, in turn, *informed* the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Albrecht*, 139 S. Ct. at 1678 (emphasis added). But agency *silence* does not "inform[]" the manufacturer of anything—particularly where, as here, the agency was not asked the relevant question to begin with. Nor is the agency's silence in any way "clear." To the contrary, "because agencies normally address problems in a detailed manner and can speak through a variety of means, . . . we can expect that they will make their intentions clear if they intend for their regulations to be exclusive." *Hillsborough*, 471 U.S. at 718. Agency *in*action, by contrast, "offers little else from which one can infer anything of an agency's intention." *Baltimore & Ohio R.R. Co. v. Oberly*, 837 F.2d 108, 115 (3d Cir. 1988).

It is for this reason that conferring preemptive power on agency silence impermissibly "expands the power of both the Executive and the Judiciary." *Lipschultz v. Charter Advanced Servs. (MN), LLC*, 140 S. Ct. 6, 7–8 (2019) (Thomas and Gorsuch, JJ, concurring in denial of certiorari). It "authorizes the Executive to make 'Law' by declining to act, and it authorizes the courts to conduct a freewheeling

judicial inquiry into the facts of federal nonregulation, rather than the constitutionally proper inquiry into whether the ordinary meanings of state and federal law conflict." *Id.* That is forbidden.

To see why, consider the Supreme Court's decision in *Sprietsma v. Mercury Marine*, 537 U.S. 51, 65 (2002)—another preemption case in which a litigant argued that agency silence or inaction should be interpreted to carry preemptive force. There, the Court considered whether a state tort claim—which stemmed from a death caused by a boat propeller—was preempted by the federal regime governing recreational boat safety and design. Before the accident, the agency had studied propeller safety but ultimately decided to "take no regulatory action to require propeller guards," because "the available accident data did not support the adoption of a regulation." *Id.* at 61. The Court rejected as "quite wrong" the argument that an agency's decision *not* to adopt a certain regulation amounts to the "functional equivalent of a regulation *prohibiting* all States and their political subdivisions from adopting such a regulation." *Id.* at 65 (emphasis added). As a result, the Court held there was no impossibility preemption.

Lower courts, too, have rejected agency silence as a basis for impossibility preemption—including when it comes to state-law failure-to-warn claims. In *Fellner v. Tri-Union Seafoods, L.L.C.*, 539 F.3d 237 (3d Cir. 2008), for example, the Third Circuit applied this principle in rejecting a manufacturer's claim of impossibility

preemption based on agency silence in the food-labeling context. In that case, a consumer diagnosed with mercury poisoning sued a manufacturer of tuna products based on the manufacturer's failure to warn of the risks of mercury poisoning. *Id.* at 240. The FDA had studied the risks of mercury in fish but had not yet required any warnings about that risk. *Id.* at 254. But that didn't mean a state-law claim on the subject could be preempted. That was because the agency's silence on the issue was not the sort of "conclusive determination" regarding what should or should not be included on a warning label that could "preempt state law." *Id.* at 254.

More broadly, the Third Circuit explained that an agency's decision to "stud[y]" or "consider[]" an issue cannot be enough to preempt state law. *Id.* at 253 ("A mere decision by the FDA not to adopt a federal warnings requirement certainly does not alone preclude states from imposing a duty to warn."); *see also Mason*, 596 F.3d at 396 (holding that the FDA's inaction in failing to mandate a warning does not amount to "clear evidence that the FDA would have rejected a label change warning about the risk"); *Dzielak v. Whirlpool Corp.*, 120 F. Supp. 3d 409, 417 (D.N.J. 2015) ("EPA's action (or rather inaction) does not rise to the level of a federal "law" that can be given preemptive effect."); *Knipe v. SmithKline Beecham*, 583 F. Supp. 2d 553, 593 (E.D. Pa. 2008) ("[T]he law is clear that express or deliberate FDA action causes preemption, not mere inaction."). Indeed, as one court explained, presuming FDA disapproval from inaction would turn the changes being effected regulation on

its head, as it would "prevent a pharmaceutical manufacturer from issuing *any* warning regarding newfound dangers associated with its already-approved drug absent an explicit FDA permission slip." *Knipe*, 583 F. Supp. 2d at 593.

The same is true here. The mere fact that the FDA did not on its own require Novartis to include a warning about the animal data (or reject any such request) cannot serve as a basis for concluding that Novartis was prohibited, by federal law, from adding that warning. And, if anything, there is even less evidence here than in *Sprietsma* or *Fellner* that the agency ever "studied" or even "considered" an animal-data-supported warning prior to saying nothing about it. The most that can be inferred from the agency's silence is that it is *possible* the warning would have been *im*possible. But that has never been sufficient for an impossibility preemption defense, and it should not be sufficient now.

CONCLUSION

The district court's decision should be reversed.

Respectfully submitted,

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