**No. 21-1517**

**IN THE UNITED STATES COURT OF APPEALS**
**FOR THE FIRST CIRCUIT**

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION

HEATHER PERHEM, 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
No. 1:15-md-02657-FDS (The Hon. F. Dennis Saylor IV)

# BRIEF OF PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF DEFENDANT-APPELLEE AND AFFIRMANCE

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## GLOSSARY

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| AAJ Amicus Br. | American Association for Justice Amicus Brief, Doc. No. 00117856012 (filed Mar. 23, 2022) |
| CBE | Changes Being Effected |
| DC Op. | June 1, 2021 Memorandum and Order issued by the District Court in this case, *reprinted at* Addendum_01 of Appellants' Addendum |
| FDA | U.S. Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |
| PAS | Prior Approval Supplement |
| PhRMA | Pharmaceutical Research and Manufacturers of America |
| Pls. Br. | Opening Brief for Plaintiffs-Appellants, Doc. No. 00117856927 (filed Mar. 16, 2022) |

## INTRODUCTION AND STATEMENT OF INTEREST

*Amicus curiae* the Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association comprised of the leading biopharmaceutical research and technology companies.[1] PhRMA members produce innovative medicines, treatments, and vaccines that save and improve the lives of countless individuals every day. PhRMA members have invested more than a trillion dollars in R&D since 2010, and in 2020 alone invested an estimated $91 billion in discovering and developing new medicines. PhRMA, 2021 Profile: Biopharmaceutical Research Industry, at 2 (2020), https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/Industry-Profile-2021/2021-Profile-3.pdf. PhRMA advocates in support of public policies that encourage the discovery of life-saving and life-enhancing new medicines.

This case presents a question of critical importance to the members of PhRMA: whether a company can be held liable for failure to warn regarding a particular alleged risk for a medicine when the FDA has been presented with

[1] Pursuant to Federal Rule of Appellate Procedure 29(a)(2), PhRMA certifies that all parties have consented to the filing of this brief. No party's counsel authored this brief in whole or in part. No party or party's counsel made a monetary contribution intended to fund the preparation or submission of this brief, and no person other than *amicus curiae*, its members, or its counsel made such a monetary contribution. Although GlaxoSmithKline LLC and former party Novartis Pharmaceuticals Corporation are members of PhRMA, they have not contributed financially to the preparation of this brief.

complete data related to that particular risk and the FDA has determined, through final agency action, that the medicine's labeling should include a different warning about that particular risk. Pharmaceutical medications are highly regulated, and the warnings that must be included for a particular medicine depend on statutorily required and carefully considered FDA judgments as to what the current science shows regarding that medication's risks and benefits. The pharmaceutical industry is also subject to increasingly massive and costly litigation centering on the same benefit-risk questions addressed by the FDA. PhRMA thus has a unique interest in ensuring that—where the FDA has determined the appropriate warning with the benefit of full information—private state-law litigation cannot be used to second-guess the FDA's decision.

## SUMMARY OF ARGUMENT

The District Court correctly held that Plaintiffs' state-law failure-to-warn claims were preempted by federal law because the FDA had, through final agency action, specified the appropriate warning for the risk of fetal injury from the prescription medicine Zofran, after being fully informed about those risks. On appeal, Plaintiffs and their amici argue that the FDA's rejection of additional birth defect warnings should not have preemptive effect because the FDA rejected proposed warnings discussing *human* data rather than warnings discussing the *animal* data that the FDA also had before it. This argument fundamentally misconstrues the nature of FDA review.

*First*, federal law vests with the FDA the ultimate responsibility for determining the nationwide warnings that must accompany medicines. In addition to requiring the FDA to review and approve or disapprove any proposed labeling change, the Food and Drug Administration Amendments Act ("FDAAA") of 2007, 21 U.S.C. § 355(o)(4), requires the FDA to update safety information in a medicine's labeling when the agency becomes aware of new information about a safety risk, and grants the FDA express authority to require such labeling changes. Under section 355(o)(4), when the FDA becomes aware of a new safety issue that it determines should be reflected in labeling for a medicine, the FDA *must* engage with the medicine's New Drug Application holder to modify the labeling as

appropriate. Conversely, if the FDA determines after evaluating the potential new safety information that no labeling modification is required, that conclusion by necessity reflects the FDA's assessment that a labeling modification is not scientifically warranted. Accordingly, Plaintiffs' speculation that the FDA might have permitted a different birth defect warning had Novartis or GlaxoSmithKline asked to warn about animal data instead of human data on the same issue cannot be squared with the FDA's statutory obligations. The FDA's rejection of Novartis's labeling supplement, despite having the Japanese animal studies pointed to by Plaintiffs before it, provides dispositive confirmation that the FDA did not believe any additional warning regarding birth defects was appropriate.

*Second*, a contrary rule would impair the FDA's ability to carry out its mission and potentially harm innovation and public health. Plaintiffs' proposed regime would both afford insufficient deference to the FDA's expert judgment and create perverse incentives for pharmaceutical manufacturers to overwhelm the FDA with never-ending labeling change requests to anticipate every possible warning iteration. Allowing liability in this situation could impair investment by subjecting manufacturers to potentially massive liability for not continually requesting warnings that the FDA has necessarily rejected. This unfair and irrational basis for liability would ultimately harm the very individuals that such expansive liability theories profess to benefit.

Accordingly, the District Court's decision should be affirmed.

## ARGUMENT

### I. Plaintiffs' Argument Fundamentally Misconstrues the Nature of FDA Review.

The FDA implements a comprehensive statutory and regulatory regime intended to ensure that pharmaceutical labeling strikes a critical balance, warning about scientifically supported risks while not diminishing those warnings by including unsupported risks. The FDA's responsibility for medicine labeling under this statutory regime includes both the duty to review warning labels proposed by manufacturers and "an independent obligation to ensure that drug labels reflect new risks" under 21 U.S.C. § 355(o)(4). *In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, No. 3:08-08 (FLW), 2022 WL 855853, at *4 (D.N.J. Mar. 23, 2022). Where, as here, the FDA has been presented with the information that Plaintiffs allege requires an enhanced warning, and the FDA decides not to impose a warning based on that information, the FDA's decision is "clear evidence" requiring preemption of Plaintiffs' failure-to-warn claims. Plaintiffs' arguments to the contrary mistake the nature of FDA review by assuming that FDA review is formulaically limited to the precise warning verbiage submitted, without the FDA actually considering the relevant issue in any meaningful way.

### A. The Comprehensive FDA Statutory and Regulatory Regime Ensures that Labeling Contains a Summary of the Essential, Scientifically Grounded Safety Information.

The FDA closely regulates the labeling for all prescription medicines, which must contain various legally-prescribed sections describing the known scientific data. Effective pharmaceutical labeling must strike a careful balance between providing information that will optimize the safe use of the medication without including unsubstantiated risk information that could undermine its safe and effective use. The FDA achieves this balance by requiring that risk information be scientifically grounded and not be polluted with scientifically unfounded risks.

Striking this proper balance is critically important, because labeling that includes unfounded safety information can lead to patient harm. First, overly long or speculative labeling may cause physicians to disregard the truly important safety information. *See, e.g.*, *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 869 (7th Cir. 2010) ("The resulting information overload [from describing every remote risk] would make label warnings worthless to consumers."); *Hood v. Ryobi Am. Corp.*, 181 F.3d 608, 611 (4th Cir. 1999) ("Well-meaning attempts to warn of every possible accident lead over time to voluminous yet impenetrable labels—too prolix to read and too technical to understand."); *Thomas v. Hoffman-LaRoche, Inc.*, 949 F.2d 806, 816 n.40 (5th Cir. 1992) (explaining that, if manufacturers were required to clutter their warnings with "every possible risk," then "physicians

[would] begin to ignore or discount the warnings"); H.R. Rep. No. 86-1861 (1960), *as reprinted in* 1960 U.S.C.C.A.N. 2833, 2837 (speculative warnings "invit[e] indifference to cautionary statements on packages of substances presenting a real hazard of substantial injury or illness"); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49,603, 49,605–06 (Aug. 22, 2008) (unjustified statements in FDA labeling may cause "more important warnings" to be "overshadow[ed]"). "The Agency regulates drug labels for precisely [this] reason: so as not to 'cause meaningful risk information to lose its significance.'" *Fosamax*, 2022 WL 855853, at *32 (citation omitted).

Second, warnings not grounded in science discourage beneficial use of medicines. *See, e.g.*, *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 391–92 (7th Cir. 2010) ("[O]verwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted …."); *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1, 14 (Cal. 2004) ("[A] truthful warning of an uncertain or remote danger may mislead the consumer into misjudging the dangers stemming from use of the product, and consequently making a medically unwise decision."); 73 Fed. Reg. at 49,605–06 ("[O]verwarning … may deter appropriate use of medical products …."); 71 Fed. Reg. 3921-3997 (Jan. 24, 2006) ("Overwarning, just like underwarning, can similarly have a negative effect on

patient safety and public health. … [A]dditional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of the Act.").

All medicines have risks, and all prescribing decisions are based on balancing those risks against the potential benefits to the patients for whom the medicine is intended. Distorting that balance by overstating unfounded or speculative risks may inhibit medical professionals from making optimal prescribing decisions.

To address these concerns, and to "help[] the public get the accurate, science-based information they need," the FDA closely regulates prescription drug labeling. Food & Drug Admin., Statement of FDA Mission, https://www.fda.gov/about-fda/what-we-do#:~:text=FDA%20Mission,-The%20Food%20and&text=FDA%20is%20responsible%20for%20advancing,maintain%20and%20improve%20their%20health. FDA regulations provide detailed labeling requirements, dictating mandatory categories, the precise content for each of those categories, and exact formatting standards. *See* 21 C.F.R. §§ 201.56–201.57, 201.80.

As part of this regime, the FDA must approve labeling before a medicine can be marketed, and it continues to review and approve labeling afterward.

Before a manufacturer can amend its labeling, it generally must obtain the FDA's approval through the submission of a "prior approval supplement" ("PAS") to its New Drug Application. *See* 21 C.F.R. § 314.70(b)(2)(v). Manufacturers can, in some circumstances, unilaterally add or strengthen a warning to reflect "newly acquired information." *Id.* § 314.70(c)(6)(iii)(A).[2] Even then, however, a manufacturer cannot distribute the new labeling until it submits a "changes being effected" ("CBE") supplement to the FDA. *See id.* § 314.70(c)(6). Unless the FDA finds that "the evidence of a causal association satisfies the standard for inclusion in the labeling," *id* § 314.70(c)(6)(iii)(A), it must retroactively reject the change and require the manufacturer to stop distributing products with the new labeling, *see id.* § 314.70(c)(6)–(7); 73 Fed. Reg. at 49,604 ("[A] CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug ….").

### B. The FDA Has an Independent Obligation to Ensure that Drug Labels Appropriately Reflect Risks.

The FDA's oversight of labeling is not limited to reactively reviewing only

[2] *See also* 21 C.F.R. § 314.3(b) ("Newly acquired information is data, analyses, or other information not previously submitted to the Agency, which may include (but is 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.").

the language put before it by a manufacturer. Under 21 U.S.C. § 355(o)(4), the FDA has an independent obligation to assess all safety information presented to it and to require safety labeling changes it deems necessary in light of any such new safety information. In particular, if the FDA "becomes aware of new safety information that [it] believes should be included in the labeling of the drug," section 355(o)(4) requires the FDA to "promptly" engage the drug's sponsor to amend the drug's labeling. *See* 21 U.S.C. § 355(o)(4)(A).

Section 355(o)(4) lays out the process for this type of FDA-directed labeling change. In response to the FDA's notification that amended labeling is required, the manufacturer may either provide proposed labeling language or notify the FDA of the reasons that it does not believe a labeling change is warranted. 21 U.S.C. § 355(o)(4)(B). In either instance, the FDA must act if it disagrees with the manufacturer's response. *See id.* § 355(o)(4)(C). Thus, even if the manufacturer provides labeling language relevant to a given risk, the FDA must still determine whether that specific language provides the appropriate means of addressing that risk, or whether alternate language would more appropriately describe the relevant safety information. *See id.* ("If the [FDA] disagrees with the proposed changes in the supplement[,] … the Secretary ***shall*** initiate discussion[] to reach agreement on whether the labeling for the drug should be modified to reflect the new safety or new effectiveness information, and if so, ***the contents of such labeling changes***."

(emphases added)). If the FDA and manufacturer continue to disagree, the FDA has a brief period to confer with the manufacturer but may then direct the manufacturer "to make such a labeling change as the [FDA] deems appropriate to address the new safety or new effectiveness information." *Id.* § 355(o)(4)(E).

Throughout this process, the FDA must fulfill its statutory obligations where it has determined a warning is required. Under the express terms of the statute, this duty extends not simply to the formalism of whether the relevant risk is addressed somewhere in the labeling, but also includes ensuring that the relevant safety information is addressed ***appropriately*** in the labeling. In no circumstance can the FDA determine that a safety risk exists and is not properly addressed in the labeling, yet do nothing. To do so would expressly violate the FDA's statutorily-mandated duty under section 355(o)(4).

Alternatively, where the FDA has made the considered scientific judgment that no modification to the labeling is required regarding a potential new safety issue, that ends the inquiry. The FDA has no obligation to alert a manufacturer regarding labeling language where the FDA has concluded that no new labeling language is warranted.

Importantly, section 355(o)(4) was added in 2007 with the intent to close a potential gap in the FDA's authority over prescription drug labeling to better protect public health. In particular, lawmakers observed that once the FDA had

identified potential safety issues for a prescription drug, it "need[ed] to be empowered … to take action to address those questions and to ensure timely notice to doctors and consumers of new safety risks that they are already taking." 153 Cong. Rec. S5628 (daily ed. May 7, 2007) (statement of Sen. Grassley); 153 Cong. Rec. S11832 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy) ("This legislation will give FDA the authority, for the first time, to compel a drug company to add warnings of newly discovered risks on the drug label."); 153 Cong. Rec. S11835 (daily ed. Sept. 20, 2007) (statement of Sen. Durbin) (noting "[t]he bill gives the FDA more tools to detect the safety problems of drugs after they are available to consumers[]" and "the FDA is given greater authority to require drug companies to add warning labels[.]"). Section 355(o)(4) was intended to provide that authority and responsibility by giving the FDA the power to affirmatively require labeling changes. *See, e.g.*, 153 Cong. Rec. S10136–37 (daily ed. July 26, 2007) (statement of Sen. Grassley) (explaining that the bill would "give FDA the much needed authorities to require labeling changes"); H.R. Rep. No. 110–225, at 4 (2007) (stating that the FDAAA "strengthens FDA's postmarket drug safety authority" by "provid[ing] FDA with the authority to require labeling changes under appropriate circumstances").

As a consequence of this statutory framework, when the FDA has been presented with relevant data and declines to require modified safety labeling, that

considered declination provides clear evidence that supports preemption of state-law failure-to-warn claims.[3] The three-Justice concurrence in *Merck Sharp & Dohme Corp. v. Albrecht* recognized precisely this statutory responsibility, explaining that the FDA's obligation to initiate a labeling change is "highly relevant" to any preemption analysis. 139 S. Ct. 1668, 1685 (2019) (Alito, J., concurring); *see also id.* at 1684 ("Under 21 U.S.C. § 355(o)(4)(A), which was enacted in 2007, Congress has imposed on the FDA a duty to initiate a label change '[i]f the Secretary becomes aware of new information, including any new safety information … that the Secretary determines should be included in the labeling of the drug.' … [T]he FDA's 'actions,' *ante*, at 1678, taken pursuant to this duty arguably affect the pre-emption analysis."). That is because, given the FDA's "duty to initiate a label change," "if the FDA declines to require a label change despite having received and considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified." *Id.* at 1684. And, as the concurrence further explained, "[n]or does

[3] The FDA's duty under section 355(o)(4)(A) applies any time it receives new information that may be relevant to safety, regardless of whether a labeling change is currently pending. *See generally* 21 U.S.C. § 355(o)(4)(B). But the FDA's obligations are heightened where, as here, it is specifically addressing a safety issue in the context of a labeling change. *See* 21 C.F.R. § 314.70(b)(2)(v); *id.* § 314.70(c)(6)–(7). For example, the FDA must perform a "complete review of the data submitted" when considering and ruling on an application. 21 C.F.R. § 314.110(a)(2).

§ 355(o)(4)(A) require the FDA to communicate to the relevant drug manufacturer that a label change is unwarranted; instead, the FDA could simply consider the new information and decide not to act." *Id.* at 1684.

Multiple courts have reached this same conclusion, recognizing that where the FDA has been made aware of relevant data, it contradicts the FDA's purpose and obligations under section 355(o)(4) to assume that the FDA ignored the import of that data simply because the agency chose not to act, or because the specific warning language requested in the regulatory arena was not worded in precisely the way that litigants argued it should be. *See, e.g.*, *In re Incretin-Based Therapies Prod. Liab. Litig.*, 524 F. Supp. 3d 1007, 1032–33 (S.D. Cal. 2021), *aff'd on other grounds*, No. 21-55342, 2022 WL 898595 (9th Cir. Mar. 28, 2022) ("[P]ursuant to 21 U.S.C. § 355 (o)(4)(a), the FDA has the authority to mandate a label change if it learns of new safety information that should be included in the labeling of a drug" and therefore "the FDA's silence on [an] issue" may be "highly relevant to its preemption analysis"); *Lyons v. Boehringer Ingelheim Pharms., Inc.*, 491 F. Supp. 3d 1350, 1360 (N.D. Ga. 2020) (explaining that, where the FDA had information in its possession and had "taken no action to update" a medication's warning label "as would be the FDA's responsibility if it was concerned about patient safety" under section 355(o)(4), the inaction "reflect[s] a rejection of the substance of Plaintiff's proposed warnings"); *Roberto v. Boehringer Ingelheim Pharms., Inc.*,

No. CPLHHDCV166068484S, 2019 WL 5068452, at *23 (Conn. Super. Ct. Sept. 11, 2019) ("[O]ne can assume that the FDA, as a public agency, will 'properly [discharge] [its] official duties' and request a label change if the circumstances warrant. … Indeed, as mentioned, the FDA has a statutory obligation to do so. *See* 21 U.S.C. § 355(o)(4)(A)." (internal quotations and citation omitted)). Indeed, on remand from the Supreme Court's decision in *Albrecht*, the United States District Court for the District of New Jersey recently explained that to assume otherwise "would effectively overlook the FDA's *raison d'etre* to regulate drug safety, its independent legal duty to notify a manufacturer as soon as it 'becomes aware of new safety information that [it] believes should be included in the labeling of a drug[,]' … and the 'presumption of regularity' accompanying its actions." *Fosamax*, 2022 WL 855853, at *27 (citing 21 U.S.C. § 355(o)(4)(A)).

Plaintiffs' preemption analysis ignores this critical framework. Plaintiffs' position amounts to an argument that, even where the relevant information has been presented to the FDA, the FDA's review of that data can never qualify as sufficient agency action for preemption unless the FDA formulaically rejects a submission containing the precise verbiage that Plaintiffs contend is appropriate. As the facts of this case illustrate, under Plaintiffs' articulation, the FDA could (1) be presented with (allegedly) new information relevant to the safety of a medication within its purview, but (2) when faced with a labeling change request

regarding the safety of that medication, *completely ignore* that relevant data and decline to require a labeling change, despite the FDA's duties under section 355(o)(4). No rational preemption framework should presume such a dereliction of agency duty. "Rather, 'in the absence of clear evidence to the contrary, [FDA officials] have properly discharged their official duties.'" *United States v. Chemical Foundation, Inc.*, 272 U.S. 1, 14-15 (1926) (quoted in *Albrecht*, 139 S.Ct. at 1684 (Alito, J., concurring)).

### C. Given its Statutory Obligation, the FDA's Rejection of Enhanced Pregnancy Warnings Regarding Birth Defects for Zofran Constitutes "Clear Evidence" for Preemption.

Given the FDA's obligation under section 355(o)(4), the FDA's 2021 approval of Novartis's Zofran labeling and corresponding decision not to require a labeling change to add an enhanced pregnancy warning regarding birth defects constitute "'clear evidence' that the FDA would not have approved [Plaintiffs' proposed birth defects] warning," *Albrecht*, 139 S. Ct. at 1676.

*First,* Novartis requested a labeling change to add an enhanced warning regarding birth defects to Zofran's labeling, which the FDA expressly rejected in April 2021. DC Op. at 29. It is undisputed that the FDA's decision on Novartis's warning language on April 29, 2021—without requesting any additional warnings based on animal data—constituted a final agency action "taken pursuant to the FDA's congressionally delegated authority." *Albrecht*, 139 S. Ct. at 1679; DC Op.

at 28-29.

*Second*, the record makes clear that, when the FDA rejected Novartis's proposed enhanced warning regarding birth defects in 2021, the agency was "fully informed" of the three Japanese animal studies that Plaintiffs contend warrant a labeling change. It is undisputed that as part of its 2019 citizen petition, GlaxoSmithKline submitted to the FDA English translations of the three Japanese animal studies, the underlying data, and peer-reviewed Japanese publications that discussed two of the three studies.[4] DC Op. at 19, 33–34, 55–56; Pls. Br. at 19. Further, representatives for GlaxoSmithKline and Plaintiffs met with the FDA in early 2020 and provided presentations to representatives from the Office of the Chief Counsel and the Office of Regulatory Policy in the FDA's Center for Drug Evaluation and Research regarding the three studies and their purported impact on Zofran's labeling requirements. *See* DC Op. at 19–21, 55–56. At the same time, as part of its PAS, Novartis also specifically referred to the three Japanese animal studies, *id.* at 55–56, attached an English translation of a peer-reviewed publication reviewing one of the three disputed studies, *id.* at 34 (Study No. 100424), and also referenced the 2019 GlaxoSmithKline citizen petition, *id.* at 23–24. In addition to

[4] Indeed, GlaxoSmithKline first notified the FDA of the studies in 1993, when it provided the FDA with the name and study number for each of the three disputed Japanese animal studies, although it did not submit copies of the studies themselves. DC Op. at 31; Pls. Br. at 14.

the animal data, Novartis again presented the FDA with the even more probative human data.

Thus, at the time the FDA denied Novartis's request for an enhanced warning regarding birth defects, the three animal studies had been brought to the FDA's attention multiple times and covered at length. Had the FDA believed that an enhanced warning regarding birth defects was necessary based on the alleged "new safety information" contained in the three studies, the FDA had a statutory obligation to "promptly" engage Novartis, the drug's then-sponsor, to amend the drug's labeling, 21 U.S.C. § 355(o)(4)(A), and to ultimately specify "the contents of [any] labeling changes" required based on that new safety information, *id.* § 355(o)(4)(C). The FDA did not do so. That decision by the FDA establishes impossibility preemption. *See, e.g.*, *In re Incretin-Based Therapies*, 524 F. Supp. 3d at 1032–33.

Nor was the FDA's action regarding the birth defect warning mere "silence," as Plaintiffs and their amici inaccurately contend. *See, e.g.*, Pls. Br. at 52; AAJ Amicus Br. at 23. Rather, the FDA's action regarding the Zofran labeling reflects an affirmative, statutorily mandated decision, which in turn constitutes "clear evidence" that the FDA would not allow the labeling changes demanded by Plaintiffs. *See, e.g.*, *Ridings v. Maurice*, 444 F. Supp. 3d 973, 991, 998 (W.D. Mo. 2020) ("[I]n light of the known issues and the ongoing give-and-take" between

manufacturers and the FDA on these issues, the FDA's decision not to require Plaintiffs' proposed labeling change "does represent clear evidence" for "impossibility preemption"); *State v. Purdue Pharma L.P.*, No. 08-2018-CV-01300, 2019 WL 3776653, at *3 (N.D. Dist. July 22, 2019) (the FDA's "continuing decision not to change [medicine's] labeling … in the face of the State's evidence and the FDA's duty to change the labeling and warnings if appropriate" required preemption).

Attempting to escape this conclusion, Plaintiffs put great weight on the fact that Novartis "did not ask FDA to consider the Japanese animal data" as part of its PAS for an enhanced pregnancy warning. Pls. Br. at 37. But because section 355(o)(4) places a duty on the FDA to amend labeling if it deems it necessary once presented with a potential serious safety issue, and because the FDA had been presented with the Japanese animal studies, it is no answer to say Novartis or GlaxoSmithKline did not use the right words or did not request the precise birth defect warning articulated by Plaintiffs. And because the FDA rejected Novartis's proposed birth defect labeling language without pursuing additional communications regarding alternate labeling language for animal studies, the FDA's rejection was necessarily grounded in *science*, not in semantics. *See, e.g.*, *Fosamax*, 2022 WL 855853, at *27 ("In other words, it is improbable that the FDA declined to approve Defendant's Precautions warning, or failed to propose a

solution to the problem it perceived with the language … all while the FDA had sufficient causal evidence [of risk,] … thus exposing patients to the risk of severe injury in the interim.").[5]

Indeed, the cases make clear that, where the FDA sees potential concern from data, the FDA acts. In the *Avandia* case Plaintiffs invoke, for example, the Third Circuit held that there was not clear evidence for preemption because the FDA had told the manufacturer that information provided to the FDA was "inadequate" and instructed the manufacturer to "amend the supplemental application" to respond to identified deficiencies. *In re Avandia Mktg., Sales & Prods. Liab. Litig.*, 945 F.3d 749, 758, 759-60 (3d Cir. 2019) (internal quotations and citation omitted). But the FDA took no such action here, either in response to GlaxoSmithKline's citizen petition or Novartis's subsequent PAS.[6] Notably, when

[5] The case law is also explicit that preemption can occur "even if the labeling change has not been presented to, and rejected by, the FDA." *Silverstein v. Boehringer Ingelheim Pharms., Inc.*, No. 19-CIV-81188, 2020 WL 6110909, at *9 (S.D. Fla. Oct. 7, 2020); *see also Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1169–70 (S.D. Cal. 2016) (the "relevant inquiry" is "whether the FDA *would* have rejected a proposed labeling change, not whether the FDA did in fact issue an explicit rejection" (emphasis added)); *Cerveny v. Aventis, Inc.*, 155 F. Supp. 3d 1203, 1213-16 (D. Utah 2016) (same), *rev'd on other grounds*, 855 F.3d 1091 (10th Cir. 2017).

[6] In fact, the FDA frequently communicates with drug manufacturers regarding new and amended labeling. The United States has described the development of labeling as "an iterative process between the applicant and the FDA" with respect to any "scientific, medical, and procedural issues that arise." Br. of United States, *Merck Sharp & Dohme Corp. v. Albrecht*, No. 17-290, 2018 WL 4562163, at *5–6 (U.S. Sept. 20, 2018) (internal quotations and citation omitted). The dynamics of

the FDA rejected GlaxoSmithKline's citizen petition in January 2021, the FDA stated that it "would 'continue to monitor and review available safety information'" regarding Zofran and "would 'take further action' if the FDA deem[ed] 'it is appropriate to do so.'" DC Op. at 22 (quoting Notice by Plaintiffs' Lead Counsel of FDA Denial of GlaxoSmithKline's citizen petition, Jan. 15, 2021, Ex. A at 16). It necessarily follows that the FDA would have taken this "further action" while addressing Novartis's later PAS, had the FDA actually deemed it "appropriate to do so."

Plaintiffs and their amici try to argue away the FDA's informed decision-making by arguing that the Novartis labeling proposal focused on *human* data, not animal data. But that distinction makes no sense. Zofran is approved for human use, and animal data is only relevant if it suggests a human risk. *See, e.g.*, *Reference Manual on Scientific Evidence* 563 (3d. ed. 2011) ("animal study results must be extrapolated to another species—human beings"); *cf. id.* ("[S]ome known teratogens in animals are not believed to be human teratogens."). Indeed, that is why the Pregnancy and Lactation Labeling Rule, 79 Fed. Reg. 72,064 (Dec. 4,

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the FDA-manufacturer relationship thus involve frequent communications throughout the tightly regulated labeling process. *See, e.g.*, 21 C.F.R. § 314.102(b) (if FDA reviewers identify "easily correctable deficiencies" in a supplement, they will "make every reasonable effort to communicate [them] promptly to applicants"). The lack of FDA outreach on the three Japanese animal studies is therefore particularly notable.

2014), which dictates the standards for pregnancy warnings for pharmaceutical medications, requires discussion of animal data. *See* 21 C.F.R. § 201.57(c)(9)(i)(B)(2) (describing requirements for pregnancy exposure risk summary based on animal data). Here, the FDA was faced with a proposed human pregnancy warning regarding birth defects, and understandably the focus was on the known human risk. But any consideration of human risk necessarily required consideration of relevant animal data, and "one can assume that the FDA, as a public agency, will 'properly [discharge its] official duties.'" *Roberto*, 2019 WL 5068452, at *23 (citation omitted). Thus, the "FDA's subsequent inaction regarding drug labeling supports the conclusion that the FDA does not consider available scientific evidence of a causal association sufficient to warrant inclusion in the labeling." *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d 1108, 1123–24 (S.D. Cal. 2015), *vacated and remanded*, 721 F. App'x 580 (9th Cir. 2017), *and adhered to*, 524 F. Supp. 3d 1007 (S.D. Cal. 2021).

Plaintiffs effectively ask the Court to second-guess the FDA's review of the science, suggesting that either the FDA ignored its statutory duty to consider new information or simply got the science wrong. But the stark implication of Plaintiffs' argument only illustrates why preemption is important here: Preemption prevents interested advocates and lay factfinders from second-guessing the FDA's expert judgment. And because state-law failure-to-warn suits center on allegations

that a warning was deficient, and do so in the context of an allegedly injured individual plaintiff, they can encourage the harmful overwarning that the FDA's extensive oversight is meant to prevent. *See Riegel v. Medtronic, Inc.*, 552 U.S. 312, 325 (2008) ("A jury … sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court."). Further, judicial decisions second-guessing the FDA's careful evaluation of data and risks threaten to seriously disrupt the FDA's efforts to regulate how and when risk information is conveyed by manufacturers, at the expense of the broader population's health and safety. *See* 153 Cong. Rec. S11,840 (daily ed. Sept. 20, 2007) (statement of Sen. Coburn) ("[T]here is an overriding Federal interest in ensuring that the FDA, as the public health body charged with making these complex and difficult scientific judgments, be the ultimate arbiter of how safety information is conveyed.").[7]

[7] The District Court assumed, and for purposes of this brief PhRMA also assumes, that the Japanese animal studies were "newly acquired information" for purposes of preemption. But there remains a meaningful question of whether these studies individually or collectively revealed any new risk "of a different type or greater severity of frequency" than the FDA was already aware. *See* 21 C.F.R. § 314.3 ("Newly acquired information … may include (but is 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*." (emphasis added)). Indeed, by rejecting an enhanced pregnancy warning in the face of the three Japanese studies that Plaintiffs trumpet, the FDA has effectively confirmed that the data from those studies, whenever and however submitted, would not meet the regulatory definition of "newly acquired

Accordingly, Plaintiffs' speculation that the FDA might have permitted an enhanced warning regarding birth defects had Novartis or GlaxoSmithKline asked in some different manner cannot be squared with the FDA's statutory obligations and the facts surrounding FDA review in this case. The FDA's rejection of Novartis's labeling supplement without initiating labeling discussion regarding the Japanese animal studies provides dispositive confirmation that the FDA did not believe any additional warning was appropriate. Because GlaxoSmithKline could not have complied with the FDA's federal directives while also including the warning Plaintiffs claim is required under state law, the District Court correctly found that Plaintiffs' claim is preempted.

## II. A Contrary Decision Would Encourage Manufacturers to Overwhelm the FDA's Review Capabilities and Hinder Innovation.

The outcome advocated by Plaintiffs is not only contrary to the statutory and regulatory framework and case law but would also have the unintended effect of impairing the FDA's ability to carry out its safety mission while potentially harming innovation and public health.

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information" because they revealed no actual different risk. If they had, the FDA would have been obligated to capture that newly revealed risk in the safety labeling. *See, e.g.*, *Knight v. Boehringer Ingelheim Pharms., Inc.*, 984 F.3d 329, 338–39 (4th Cir. 2021) (explaining that, where the FDA was already aware of and had analyzed the risk, even if there is a "'new analysis of previously submitted data,' it does not 'reveal risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA'" and is therefore not newly acquired information (quoting 21 C.F.R. § 314.3(b))).

As it is, Novartis and GSK have more than adequately notified the FDA with information and requests for consideration of enhanced Zofran warnings. Under the regime proposed by Plaintiffs, manufacturers would instead be encouraged to paper the FDA with labeling change requests that address every possible combination of warning language a plaintiff could conceivably articulate, regardless of whether the information underlying the proposed warning language has already been provided to the FDA. *See, e.g.*, *Seufert*, 187 F. Supp. 3d at 1175 ("A rule to the contrary would encourage prophylactic labeling changes by manufacturers, which, in turn, could inundate the FDA with labeling submissions."). If followed, this directive would divert the FDA's resources away from the study of new potential safety issues in favor of defending decisions it had effectively already made. Diverting the attention of the FDA toward litigation-defensive submissions would place an excessive burden on the agency. *See* 71 Fed. Reg. at 3,934 ("FDA reviews all … submissions …."); *Lofton v. McNeil Consumer & Specialty Pharms.*, 672 F.3d 372, 380 (5th Cir. 2012) (when manufacturers are compelled "to flood the FDA with information" to protect against liability, the FDA "loses control over its ability, based on scientific expertise, to prescribe—and intelligently limit—the scope of disclosures necessary for its work"); Br. for the United States as *Amicus Curiae* Supporting Pet'r at 25, *Wyeth v. Levine*, No. 06-1249, 2008 WL 2308908 (U.S. June 2, 2008) ("[The

FDA] could not reasonably be expected to expressly reject every possible variant of approved labeling as part of its decisional process. Indeed, it would underestimate the post hoc imagination of lawyers to think such an exhaustion of potential variants by the manufacturer or the agency is even possible."). The FDA's resources should not be expended on unnecessary and duplicative labeling requests simply to ensure that the agency's scientific judgments are enforced in the courts. *See Wyeth v. Levine*, 555 U.S. 555, 578 (2009) ("FDA has limited resources to monitor the 11,000 drugs on the market ….").

Indeed, the Supreme Court recognized precisely this concern in *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 341 (2001), where the Court held that state law "fraud-on-the-FDA" claims are preempted. *Id.* The Court reasoned that such claims incentivize manufacturers "to submit a deluge of information that the [FDA] neither wants nor needs" out of "fear that their disclosures … will later be judged insufficient in state court," thereby creating "additional burdens on the FDA[]." *Id.* at 351. The preemption standard advocated by Plaintiffs creates the same incentives that *Buckman* found intolerable.

The unique facts of this case illustrate this concern. In addition to the FDA undertaking multiple labeling reviews regarding the relevant risk—use of Zofran during pregnancy—both the Defendant in this case and *Plaintiffs' lawyers themselves* took the unusual step of meeting with the FDA to present their views

on the science being litigated in these lawsuits. If every set of litigants in a pharmaceutical lawsuit took such a step, and if the defendants in those lawsuits further had to formally propose to the FDA every variant of labeling that plaintiffs and their counsel might propose, the FDA would be rapidly overwhelmed by attempting to address plaintiff litigation arguments rather than scientific data.

At the same time, allowing liability because a company elects *not* to paper the FDA with every conceivable warning iteration may harm innovation and thus harm public health. Developing new medicines is an expensive endeavor, requiring massive investments of resources. *See, e.g.*, J.A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20, 25 (2016) (estimated average industry cost of new prescription drug approval, inclusive of failures and capital costs, is $2.59 billion). As the Tenth Circuit observed in the context of medical devices, "[r]equiring manufacturers to comply with fifty states' warning requirements … on top of existing federal … warning requirements, might introduce sufficient uncertainty and cost that manufacturers would delay or abandon at least some number of life-saving innovations." *Caplinger v. Medtronic, Inc.*, 784 F.3d 1335, 1346 (10th Cir. 2015).

Plaintiffs' proposed rule would thus incentivize manufacturers to flood the FDA with duplicative requests to avoid litigation, overburdening the FDA,

contravening the public policy goals inherent in the FDA's warnings review process, and ultimately harming patients.

## CONCLUSION

For the foregoing reasons, the Court should hold that the FDA's fully informed decision not to require a labeling change to add an enhanced warning regarding birth defects is "'clear evidence' that the FDA would not have approved [the] warning," *Albrecht*, 139 S. Ct. at 1676 (quoting *Wyeth*, 555 U.S. at 571), and the District Court's judgment should be affirmed.

Respectfully submitted,

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May 23, 2022

## CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Brief complies with the type-volume limitations of Rules 29(a)(5) and 32(a)(7)(B) of the Federal Rules of Appellate Procedure because it contains 6,493 words, excluding the parts of the brief exempted by Rule 32(f). I further certify that this Brief complies with the typeface requirements of Rule 32(a)(5) and the type-style requirements of Rule 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Word in 14-point Times New Roman font.

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May 23, 2022

**CERTIFICATE OF SERVICE**

I hereby certify that on May 23, 2022, I caused the foregoing Brief to be filed with the Clerk of the U.S. Court of Appeals for the First Circuit using the appellate CM/ECF system and to be served upon counsel for all parties via the CM/ECF system.

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