United States Court of Appeals
For the First Circuit

No. 21-1517

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.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

[Hon. F. Dennis Saylor, IV, U.S. District Judge]

Before

Kayatta and Howard, Circuit Judges,
and Walker, District Judge.*

Louis M. Bograd, with whom Motley Rice LLC was on brief, for appellants.

Lisa S. Blatt, with whom Amy Mason Saharia, J. Matthew Rice, Jami M. King, Williams & Connolly LLP, Scott A. Chesin, and Shook,

* Of the District of Maine, sitting by designation.

Hardy & Bacon, were on brief, for appellee GlaxoSmithKline LLC.

Matthew W.H. Wessler, Joanne Grace Dela Peña, Gupta Wessler PLLC, Ellen Noble, and Public Justice on brief for amici curiae American Association for Justice and Public Justice.

Emily Ullman, Michael X. Imbroscio, Nicole Antoine, Paul W. Schmidt, and Covington & Burling LLP on brief for amicus curiae Pharmaceutical Research and Manufacturers of America.

January 9, 2023

KAYATTA, Circuit Judge. This appeal arises out of multidistrict litigation concerning the pharmaceutical drug ondansetron hydrochloride (better known by its brand name, Zofran), which is commonly taken off-label during pregnancy. Plaintiffs claim that GlaxoSmithKline (GSK), the company responsible for initially putting Zofran on the market and for manufacturing the drug until 2015, should be held liable under various state product liability laws for failing to warn consumers that animal studies revealed adverse effects on the fetus, including birth defects -- a warning that does not appear on Zofran's federally approved label. The district court granted summary judgment in favor of GSK, finding that federal law preempted plaintiffs' state law claims because there was clear evidence that the Food and Drug Administration (FDA) would have rejected the warning that plaintiffs allege is required under state law. We affirm the district court's grant of summary judgment. Our reasoning follows.

I.

A.

We begin by detailing the complex federal regulatory scheme governing pharmaceutical drug labels. Congress enacted the Food, Drug, and Cosmetic Act (FDCA) in 1938 "to bolster consumer protection against harmful products." Wyeth v. Levine, 555 U.S. 555, 574 (2009); see 21 U.S.C.A. §§ 301 et seq. Pursuant to that

statute, drug companies cannot sell or market a new pharmaceutical drug product without prior approval from the FDA. See 21 U.S.C. § 355(a). To obtain this approval, a manufacturer (also commonly referred to as the drug's sponsor) must submit comprehensive information about the drug to the FDA in a New Drug Application. See id. § 355(b)(1). During this process, the FDA reviews a drug's safety and efficacy as well as the drug's proposed labeling. See id.

The FDA extensively regulates the format and substance of the information that appears on a drug's label. See, e.g., 21 C.F.R. §§ 201.56, 201.57. In so doing, one of its objectives is to "prevent overwarning, which may deter appropriate use of medical products, or overshadow more important warnings." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49603, 49605–06 (Aug. 22, 2008). It therefore "allow[s] only information for which there is a scientific basis to be included in the FDA-approved labeling." Id. at 49604. And it guards against the "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008).

The FDA also has an extensive set of regulations governing the use of drugs during pregnancy. To obtain FDA

approval for any such use, a drug's sponsor must include in its application, among other things, an "integrated summary of the toxicological effects of the drug in animals," including "tests of the drug's effects on reproduction and the developing fetus." 21 C.F.R. § 312.23(a)(8)(ii)(a).

At the time Zofran was initially approved by the FDA, the FDA classified drugs into five categories of safety for use by pregnant people: A, B, C, D, and X. See 21 C.F.R. § 201.57(c)(9)(i)(A) (2006). Each category came with a standardized set of warnings. Id. Under the then-applicable regulations, if animal studies "failed to demonstrate a risk to the fetus and there [were] no adequate and well-controlled studies in pregnant women," the drug would be classified into Pregnancy Category B and include the following label:

> Pregnancy Category B. Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

21 C.F.R. § 201.57(c)(9)(i)(A)(2). If, however, animal studies "show[ed] an adverse effect on the fetus, if there [were] no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable

despite its potential risks," the drug would be categorized into Pregnancy Category C. 21 C.F.R. § 201.57(c)(9)(i)(A)(3). The label would then need to include the following statement:

> Pregnancy Category C. (Name of drug) has been shown to be teratogenic[1] (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Id. In Category C, the label "must contain a description of the animal studies." Id.

The current regulations, promulgated in 2014 as the Pregnancy and Lactation Labeling Rule (PLLR), no longer use risk categories for pregnancy-drug labels. See Requirements for Pregnancy and Lactation Labeling, 79 Fed. Reg. 72064, 72076-77 (Dec. 4, 2014). Instead, the PLLR requires that labels contain a risk statement summarizing animal and human studies, with distinct subsections describing animal and human data. See id.

After the FDA approves a label for a drug, that label is not immutable. That is because knowledge about a drug's safety and efficacy can change over time. Accordingly, the FDA provides several pathways for a drug manufacturer, citizen, or the agency itself to make changes to a drug's label.

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[1] Teratogenicity refers to a drug's ability to cause defects in a developing fetus.

First, a drug manufacturer can file a Prior Approval Supplement (PAS) with the FDA to request revisions to a label. See 21 C.F.R. § 314.70(b). The PAS procedure resembles the process for obtaining initial approval for the drug's label and requires the FDA to approve the change in the label before it can be made.

Second, a drug manufacturer can use the Changes Being Effected (CBE) regulations to unilaterally amend a label and seek after-the-fact approval from the FDA. See 21 C.F.R. § 314.70(c)(6)(iii). The CBE procedure permits manufacturers to change a label "to reflect newly acquired information" if the changes "add or strengthen a . . . warning" for which there is "evidence of a causal association." Id.; see also 21 C.F.R. § 201.57(c)(6). Although a manufacturer initiates this process, "the FDA reviews CBE submissions and can reject label changes even after the manufacturer has made them," and "manufacturers cannot propose a change that is not based on reasonable evidence." Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668, 1679 (2019).

Third, the FDA permits private individuals and organizations to request changes to a drug's label based on "reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 201.80(e); see 21 C.F.R. § 10.30(b)(3); Cerveny v. Aventis, Inc., 855 F.3d 1091, 1102 (10th Cir. 2017).

Fourth, the FDA, on its own initiative, must notify a drug manufacturer of the need to submit a supplement proposing

changes to a drug's label if the FDA becomes aware of new information, including safety information, that it determines should be included in the drug label. 21 U.S.C. § 355(o)(4)(A), (B).

B.

With this regulatory background in mind, we walk through the events that gave rise to the present appeal. Zofran is an FDA-approved prescription drug for the prevention of chemotherapy-induced, radiation-induced, and post-operative nausea and vomiting. Although Zofran has never been approved for preventing pregnancy-related nausea and vomiting, it is often prescribed off-label for that purpose. GSK owned Zofran from 1991, when the drug first received FDA approval, until 2015, when GSK sold the rights to manufacture and market the drug to the pharmaceutical company Novartis. Zofran remains on the market, and its label does not currently warn of an association between its use and pregnancy-related risks, including birth defects.

As part of Zofran's New Drug Application approval process in 1990 and 1991, GSK submitted data related to Zofran's safety and efficacy to the FDA. The data included a set of four animal reproductive studies conducted on rats and rabbits in the United Kingdom (study nos. R10590 (UK Oral Rat Study), and R10937 (UK IV Rat Study), L10649 (UK Oral Rabbit Study), L10873 (UK IV Rabbit Study)). Although the investigators in those studies

observed some incidences of birth defects among the animal subjects, the studies did not conclude that there was a causal association between Zofran and birth defects. In brief, defects can and do occur in the absence of Zofran, and the studies did not reveal a statistically significant gap between the number of defects seen in subjects treated with Zofran and the control groups. The FDA, in an internal pharmacological review associated with the approval of Zofran, assessed the four UK animal studies and concluded that the drug did not induce a teratogenic effect.

GSK also sponsored animal studies in Japan in the late 1980s to satisfy Japanese regulatory requirements. These studies included three rat and rabbit reproductive studies (study nos. 100422 (Japan Submitted Oral Rat Study), 100424 (Japan IV Rat Study), and 100441 (Japan Oral Rabbit Study)) and a preliminary animal study designed to select appropriate dosages (study no. 100423 (Japan Preliminary Dosage Study)), all of which GSK characterizes in this appeal as "parallel" to the UK studies. The Japanese studies used the same types of animals (rats and rabbits) and the same formulations of the drug (oral and intravenous) as the UK studies. None of these studies, however, were included in GSK's New Drug Application filed with the FDA.[2] As will become

[2] The studies were disclosed by name and number in a list with dozens of other studies in a 1993 GSK annual report published after Zofran was approved. That report described the studies as "[s]tudies performed specifically to satisfy Japanese regulatory

clear, plaintiffs focus their appeal on the three Japanese studies not originally submitted to the FDA: the Japan Preliminary Dosage Study, the Japan IV Rat Study, and the Japan Oral Rabbit Study.

When Zofran was first approved by the FDA, it was categorized into Pregnancy Category B, because animal studies had not shown evidence of teratogenicity (under the then-applicable risk categorization regulations). The next designation, Pregnancy Category C, would have been appropriate if, among other things, animal studies had shown that the drug was teratogenic -- i.e., that the drug was causally related to birth defects when taken during a pregnancy. The FDA ultimately approved four additional New Drug Applications for varying Zofran formulations in 1992, 1995, 1997, and 1999, classifying each in Pregnancy Category B.

In 1997, in connection with the New Drug Application for one of Zofran's formulations (the oral solution), GSK submitted a translated version of the Japan Submitted Oral Rat Study to the FDA. The FDA, in an internal pharmacological review that included an assessment of that study, noted that Zofran "was not teratogenic." In that same review, the FDA also explained that the results in that study were "comparable to those [in the] teratogenic study in female rats that was included in the original submission." The oral solution formulation of Zofran, like the

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requirements" and as "either repetitive or provid[ing] no new significant safety information."

other formulations, was classified into Pregnancy Category B. GSK did not submit the Japan Preliminary Dosage Study, the Japan IV Rat Study, or the Japan Oral Rabbit Study with any of the New Drug Applications for the various formulations of Zofran.

Over the next several years, the FDA reviewed a number of requests for label changes to Zofran related to the potential link between Zofran and birth defects, as outlined below.

2010 FDA Review. In 2010, because of its awareness of the frequency with which Zofran was used during pregnancy, the FDA asked GSK to review and analyze the literature on the use of Zofran during pregnancy and provide an assessment of the data. The FDA also requested that GSK propose labeling changes to Zofran if needed through the PAS procedure. GSK responded in 2011, concluding that it "d[id] not believe there [wa]s sufficient evidence to warrant a change" to the label. The FDA did not conduct further action related to this request.

2013 Reichmann Citizen Petition. In 2013, James Reichmann, a private individual, submitted a citizen petition asking the FDA to revise Zofran's pregnancy-related labeling and to reclassify Zofran's pregnancy category. The FDA rejected the petition, concluding that the totality of the data it had at the time "d[id] not support a conclusion that there is an increased risk of fetal adverse outcomes." The Japanese animal studies were

not provided to the FDA or referenced in connection with the 2013 citizen petition.

2015 Novartis PAS. In 2015, after Novartis acquired Zofran from GSK, Novartis assumed responsibility for amending Zofran's label to conform with the PLLR, the pregnancy labeling regime that replaced the prior risk categorization system. Using the PAS process, Novartis proposed a set of warnings advising against use of Zofran during pregnancy, based on published human data suggesting the possibility of an increased risk of major birth defects or congenital malformations associated with such use. Novartis did not refer to the Japanese animal studies.

The FDA rejected the labeling proposals. In particular, the FDA rejected Novartis's proposal to add the following language: "Animal studies are not always predictive of human response, therefore, the use of ondansetron in pregnancy is not recommended." The agency explained: "We do not agree with keeping this statement in labeling based on the available human information." Novartis and the FDA engaged in additional rounds of revisions before the FDA approved the new Zofran label in 2016. The approved label indicated that "[a]vailable data do not reliably inform the association of ZOFRAN and adverse fetal outcomes" and that "[r]eproductive studies in rats and rabbits did not show evidence of harm to the fetus."

2019 GSK Citizen Petition. In 2019, GSK filed its own citizen petition with the FDA to obtain clarification from the agency on whether the information identified by plaintiffs in their suit "contain[ed] any new and material information about Zofran" that would necessitate a change to the drug's label. The petition sought review of, among other things, translated versions of the Japan Preliminary Dosage Study, the Japan IV Rat Study, and the Japan Oral Rabbit Study -- the studies plaintiffs rely on -- by the FDA for the first time. GSK requested that the FDA "either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling" in light of the information submitted with the petition.

In 2021, the FDA denied GSK's citizen petition, refusing to undertake any updated analysis regarding the label. It explained that GSK's "request that FDA review and opine on certain pieces of information to answer a hypothetical question separate and apart from FDA's ongoing product review . . . would detract from fulfilling the Agency's statutory obligations" and "is not the appropriate subject of a citizen petition." Thus, the FDA expressly "decline[d] to conduct the evaluation [GSK] request[ed] related to the . . . information at issue in the litigation."

2020 Novartis PAS. While GSK's citizen petition was pending, Novartis submitted a PAS to the FDA based on "recently published [human] epidemiological studies." Novartis proposed

changes to the Risk Summary and Human Data sections of the Zofran label to account for the new epidemiological studies. It did not, however, propose any changes to the Animal Data or Risk Summary sections reflecting findings from animal data.[3]

In response to Novartis's PAS, the FDA noted that "[g]iven the inconsistency in published findings and the limitations in the design of [human epidemiological] studies, an increased risk of fetal orofacial clefts[4] from maternal ondansetron use cannot be concluded." After another round of communications in which Novartis proposed to warn that an association between Zofran and birth defects "cannot be ruled out," the FDA repeated that "[g]iven inconsistencies in the results of published epidemiological studies on the association between ondansetron use and major birth defects, we are not able to make any conclusions regarding the safety of ondansetron use in pregnancy." The FDA did permit Novartis to include a proposed paragraph in the Human Data section discussing the fact that "[s]everal studies have

[3] In documentation submitted concurrently with the PAS, Novartis did inform the FDA that Zofran "did not affect embryo-fetal development in the rat or rabbit [studies] and had no adverse effects on fertility or on the general reproductive performance and the post-natal development of rats." In so doing, it discussed a recent study by plaintiffs' expert Dr. Bengt Danielsson as well as two peer-reviewed articles discussing the Japanese animal studies at issue here.

[4] Orofacial clefts are openings or slits in the upper lip (cleft lip), roof of the mouth (cleft palate), or both.

assessed ondansetron and the risk of oral clefts with inconsistent findings."

The final approved label from the Novartis PAS also included (unchanged from the previous version of the label) a sentence in the Risk Summary portion of the label that reads: "Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered intravenously during organogenesis at approximately 3.6 and 2.9 times the maximum recommended human intravenous dose of 0.15 mg/kg given three times a day, based on body surface area, respectively." Novartis did not propose changes to either the Risk Summary or the Animal Data section of Zofran's label based on animal studies. Nor did Novartis or the FDA comment specifically on animal studies during the PAS process.

C.

In 2015, various plaintiffs filed separate suits in federal court alleging that the use of Zofran during pregnancy caused birth defects. These suits were based in part on the theory that GSK engaged in an intentionally misleading plan to market Zofran for pregnancy in violation of state law by failing to warn that animal studies showed the drug's potential to harm pregnant people and fetuses when ingested during pregnancy. The Judicial Panel on Multidistrict Litigation created a multidistrict

litigation proceeding for the individual suits, assigning the case to the District of Massachusetts.

Eyeing a potential conflict between plaintiffs' state law claims and the federal labeling scheme described above, GSK moved for summary judgment before the district court on preemption grounds, arguing that federal law preempts all of plaintiffs' state law failure-to-warn claims. In February 2019, the district court denied GSK's motion for summary judgment, concluding that preemption raised issues of fact for the jury as to whether the Japanese animal studies were newly acquired information and whether there was clear evidence that the FDA would not have approved the warnings sought by plaintiffs. However, after the district court's decision, the Supreme Court decided Albrecht, which held that at least one portion of the preemption question is a matter of law for the judge to decide and not a matter of fact to be reserved for the jury. See 139 S. Ct. at 1679. Accordingly, the district court vacated its prior decision in part and allowed GSK to renew its motion for summary judgment, which GSK did.

In June 2021, the district court granted GSK's renewed motion for summary judgment, holding that federal law preempts plaintiffs' state law claims. Plaintiffs timely appealed.

II.

We review an order granting summary judgment de novo. Alston v. Town of Brookline, 997 F.3d 23, 35 (1st Cir. 2021). In

so doing, "we evaluate the facts of record in the light most flattering to the nonmovant . . . and draw all reasonable inferences in that party's favor." Id.

III.

This appeal broadly asks one critical question: Whether federal law preempts plaintiffs' state law claims that GSK should have warned both prescribing doctors and pregnant people that "animal studies showed harm to the fetus when Zofran was ingested during pregnancy." The Supremacy Clause provides that federal law "shall be the supreme Law of the Land; . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. Accordingly, "[f]ederal law impliedly preempts state law 'where it is "impossible for a private party to comply with both state and federal requirements."'" In re Celexa & Lexapro Mktg. & Sales Pracs. Litig., 779 F.3d 34, 40 (1st Cir. 2015) (quoting Mut. Pharm. Co. v. Bartlett, 570 U.S. 472, 480 (2013)). The Supreme Court has instructed that preemption based on impossibility is a "demanding defense." Wyeth, 555 U.S. at 573. The district court assigned the burden of establishing impossibility to the defendant. Neither party challenges that assignment. See, e.g., Albrecht, 139 S. Ct. at 1678 (referring to preemption as a "defense" requiring the manufacturer to show that federal law prohibited making plaintiffs' proposed label changes).

On appeal, plaintiffs contend that GSK failed to carry its burden of establishing impossibility. In support of this contention, plaintiffs advance a two-step argument. First, they argue that GSK has failed to show that it could not have employed the CBE procedure to change its label by treating the previously undisclosed Japanese animal studies as "newly acquired information." Second, plaintiffs argue that "none of the FDA's actions [once fully informed] constitute clear evidence that the FDA would have rejected a stronger pregnancy warning concerning the animal study data." We consider each step in turn.

A.

The parties dispute whether GSK ever possessed newly acquired information that would have justified unilaterally changing Zofran's label under the CBE procedure to disclose that animal studies indicated that the drug was teratogenic. In theory, this dispute poses a bit of a conundrum: Must we determine whether the information qualifies as newly acquired information, or must we ask whether there is clear evidence that the FDA would have rejected a CBE change because the information is not newly acquired? Under the former inquiry, if a court finds as a threshold matter that there is no newly acquired information, then the failure to invoke the CBE procedure creates no bar to a

preemption defense.[5] But, if the latter inquiry were called for, it would be quite difficult (although not impossible) to obtain clear evidence of the FDA's position in the form of "agency action carrying the force of law," Albrecht, 139 S. Ct. at 1679, in cases where the manufacturer never invoked the CBE procedure (perhaps because the manufacturer reasonably did not believe the information was newly acquired).

Albrecht can arguably be read as implying a middle ground, deeming the CBE procedure unavailable if there is no reasonable basis for treating the information identified by plaintiffs as newly acquired information. 139 S. Ct. at 1679 (noting that "manufacturers cannot propose a change that is not based on reasonable evidence").

In this particular case, we need not determine definitively whether a judicial finding of newly acquired information serves as a threshold prerequisite for determining that the CBE procedure was available to GSK. All parties presume that it so serves. Plaintiffs in particular repeatedly accept and present the framing of their argument as contingent in its first "step" on a finding that the Japanese animal studies constituted

[5] The Fourth Circuit recently adopted this inquiry as controlling, finding the CBE procedure unavailable based on the court's determination that the information at issue was not newly acquired. See Knight v. Boehringer Ingelheim Pharms., Inc., 984 F.3d 329, 339-41 (4th Cir. 2021).

"newly acquired information." See, e.g., Appellant's Br. 28 ("Plaintiffs' argument proceeds in . . . steps. First, the Japanese animal studies . . . are 'newly acquired information.'").

Thus, we turn to assessing whether the three Japanese animal studies identified by plaintiffs constituted "newly acquired information" that would have permitted GSK to make use of the CBE procedure to unilaterally change Zofran's label (subject to after-the-fact FDA approval) in line with what plaintiffs allege is required under state law.[6] Following the parties' lead, we proceed under the assumption that determining whether certain information is "newly acquired" is a legal question. See Knight v. Boehringer Ingelheim Pharms., Inc., 984 F.3d 329, 337–38 (4th Cir. 2021) (concluding that preemption is a question of law that is reviewed de novo, and proceeding to determine, as part of its preemption analysis, whether data was "newly acquired information").[7]

[6] The district court assumed without deciding that the information in the Japanese animal studies was "newly acquired," ultimately holding that plaintiffs' claims were preempted on other grounds.

[7] The Supreme Court has seemingly left open the question whether what constitutes "newly acquired information" is a question of law or a question of fact. In relevant part, Albrecht holds only that "the question of agency disapproval" in the evaluation of "clear evidence" under Wyeth is a question of law that a judge must decide. Albrecht, 139 S. Ct. at 1679. In reaching this conclusion, the Court pointed to factors that are specific to the question of "clear evidence." Id. at 1680 (noting that judges rather than juries are "better equipped to evaluate

The CBE procedure is available for "[c]hanges in [a drug's] labeling to reflect newly acquired information" in order "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c)." 21 C.F.R. § 314.70(c)(6)(iii)(A). The FDA regulations specify that "labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57(c)(6)(i). The regulations define "newly acquired information" to mean:

> 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.

21 C.F.R. § 314.3(b). This includes, among other things, "an increasing body of data of an inherent risk with the drug" and "new data from a clinical study evincing [a drug's] inefficacy." Celexa, 779 F.3d at 42.

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the nature and scope of an agency's determination").

Plaintiffs argue that the Japanese animal studies constitute "newly acquired information" under the CBE regulations for three reasons: (1) the studies reveal evidence of teratogenicity that the animal studies GSK provided to the FDA did not; (2) the studies are meaningfully different from the UK studies; and (3) plaintiffs' regulatory expert Dr. Brian Harvey opined that the studies constitute "newly acquired information." We consider each reason in turn.

1.

Plaintiffs first assert that the three originally non-disclosed Japanese animal studies reveal evidence of teratogenicity that the prior studies disclosed to the FDA did not. There is no dispute that GSK had previously submitted to the FDA four animal studies conducted in the UK and one animal study conducted in Japan. And all agree that, after reviewing the previously submitted studies, the FDA concluded that Zofran belonged in Pregnancy Category B. Accordingly, GSK could have changed its label pursuant to the CBE regulations only if the Japanese studies touted by plaintiffs revealed "risks of a different type or greater severity or frequency" than those identified in the previously submitted studies and also provided "reasonable evidence of a causal association" between Zofran and birth defects. See 21 C.F.R. §§ 201.57(c)(6)(i), 314.3(b).

Plaintiffs make three assertions as to why the Japanese animal studies reveal evidence of teratogenicity not found in the prior studies. According to plaintiffs, the studies reveal: an increase in embryofetal death in the 10 mg/kg IV treatment group of rats compared to the control group in the Japan Preliminary Dosage Study; an increase in embryonic death and increased incidences of major external malformations, including ventricular septal defects (a kind of heart defect), in the 10 mg/kg IV treatment group of rats compared to the control group in the Japan IV Rat Study; and an increase in skeletal defects in the 2.5 and 10 mg/kg oral treatment groups of rabbits compared to the control group in the Japan Oral Rabbit Study. These results, plaintiffs argue, are reasonable evidence of a causal association between Zofran and birth defects and demonstrate risks greater in number, magnitude, and kind than the studies previously presented to the FDA.

The first problem for plaintiffs is that the risks they identify in the three Japanese studies -- embryofetal death, major malformations including ventricular septal defects, and skeletal defects -- were not found by the researchers in those studies to be attributable to Zofran. For instance, in the Japan Preliminary Dosage Study, the investigators concluded that in the "10 mg/kg [treatment] group, there were no embryolethal, growth suppressive and teratogenic . . . effects on the fetuses." So, although the

number of embryofetal deaths was greater in a treatment group compared to the control group in that study, the researchers nonetheless found that there was no statistically significant difference between the groups. Similarly, although the Japan IV Rat Study revealed instances of malformations, including ventricular septal defects in two fetuses in the 10 mg/kg treatment group, the researchers again concluded that "[n]o significant differences were found between the [treatment] groups and the control group in the total number of fetuses with the above anomalies or variations and in . . . each incidence of these findings." And, with respect to skeletal anomalies, in the Japan Oral Rabbit Study, the investigators observed that "[t]he effects of [treatment] were not observed in the incidences of external, visceral or skeletal anomalies and variations in fetuses, and there were no findings indicating the teratogenicity of [the treatment]."

To be sure, the relevant FDA regulations explain that, with respect to determining whether "evidence of a causal association" exists for purposes of the CBE regulations, 21 C.F.R. § 314.70(c)(6)(iii), "a causal relationship need not have been definitely established" and only "reasonable evidence of a causal association" between a risk and a drug need be shown. 21 C.F.R. § 201.57(c)(6)(i). However, each of the three studies to which plaintiffs point concluded that there was no statistically

significant relationship between Zofran and observed birth defects in animal subjects -- that is, the studies concluded that incidences of birth defects were within the background range expected to occur naturally in the subjects. Plaintiffs fail to explain why this is any evidence at all of a causal association between Zofran and birth defects, much less "reasonable evidence" of such an association.

In any event, the second problem for plaintiffs is that the risks flagged by the Japanese animal studies were all known to the FDA at the time of its categorization of Zofran into Pregnancy Category B. The studies GSK submitted to the FDA for consideration in the 1990s -- the four UK studies and one Japanese study -- used the same combinations of animals (rats and rabbits) and administration methods (oral and intravenous) as the three Japanese studies flagged by plaintiffs. The UK IV Rabbit Study, like the Japan Preliminary Dosage Study, observed an increase in embryofetal deaths. The Japan Submitted Rat Study likewise reported one instance of a ventricular septal defect (in line with the two reported the Japan IV Rat Study, but like the Japan IV Rat Study, the researchers concluded that it was within the background incidence range. As for skeletal defects, three of the studies submitted to the FDA (the UK Oral Rat Study, the UK Oral Rabbit Study, and the UK IV Rabbit Study) reported decreased skeletal

ossification, but none of those studies found these skeletal defects to be associated with Zofran.

Thus, the three Japanese studies at issue do not appear to "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA" as required to meet the definition of "newly acquired information." 21 C.F.R. § 314.3(b); cf. Knight, 984 F.3d at 338 (concluding that an academic paper discussing the correlation between a drug and a risk was not "newly acquired information" because "the FDA was already aware of this correlation"). Although we understand that "risk information accumulates over time," Wyeth, 555 U.S. at 569, and "newly acquired information" can include a new analysis of preexisting data "showing risks of a different type or of greater severity or frequency," id., the Japanese studies neither offer nor invite any such new analysis.

2.

Plaintiffs next argue that the Japanese animal studies at issue are different in kind from the UK studies considered by the FDA because the Japanese studies used higher dosing levels, which more closely approximate human exposure levels. Plaintiffs explain that the animals in the UK studies were insufficiently dosed to approximate human exposure levels. However, even if the Japanese animal studies better approximated human exposure levels than the UK studies did, plaintiffs still do not explain why the

Japanese studies revealed different or more severe risks than the information already provided to the FDA. Indeed, in each of the three Japanese studies plaintiffs point to, the investigators concluded that the observed anomalies in the animal subjects were not dose related and there was no evidence of teratogenicity. Finally, the Japanese study that was submitted to the FDA, which used higher dosages presumably more in line with what plaintiffs think is appropriate (and certainly higher than the corresponding UK study), found that incidences of the observed fetal anomalies had no dose-dependency and that Zofran was not teratogenic. Accordingly, we are not persuaded that the difference in dosages alone makes the Japanese studies highlighted by plaintiffs "newly acquired information."

3.

Lastly, plaintiffs point out that their regulatory expert, Dr. Brian Harvey, a former FDA official, opined that the Japanese animal studies would constitute "newly acquired information" under the CBE regulations. As previously noted, like the parties, we treat the question of whether the studies constitute newly acquired information as a question of law. Expert testimony on questions of law "is rarely admissible" because such testimony "cannot properly assist the trier of fact." Nieves-Villanueva v. Soto-Rivera, 133 F.3d 92, 100 (1st Cir. 1997) (second quoting Burkhart v. Wash. Metro Area Transit Auth., 112 F.3d 1207,

1212 (D.C. Cir. 1997)). To that end, Dr. Harvey's opinion is likely inadmissible. Although experts can opine on the underlying factual questions, including providing interpretations of pharmaceutical studies, they provide little, if any, relevant assistance when they opine on the ultimate legal question of whether something is "newly acquired information." And, even if we were to consider Dr. Harvey's opinion on this question, it would not enable us to conclude that the Japanese animal studies constituted newly acquired information. Dr. Harvey could not say that he had even looked at the reports GSK submitted in 1990 to the FDA in connection with the original label approval and was uncertain as to whether he even reviewed the Japanese studies. His opinion, moreover, was that all animal studies should have been reported to the FDA, irrespective of their content. Correct or not, such an opinion sidesteps the question whether the content of the studies constituted the type of evidence that would enable the manufacturer to invoke the CBE procedure.

* * *

As a final stretch in their first step, plaintiffs appear to suggest that it is not the three Japanese animal studies themselves that reveal new risks. Rather, it is their scientific expert Dr. Bengt Danielsson's 2018 interpretation of those studies, in conjunction with the prior studies presented to the FDA and Dr. Danielsson's research on related drugs, that show the

full extent of Zofran's teratogenicity. There are at least three flaws with this approach. The first is one of timing -- Dr. Danielsson's expert report was not prepared, and thus not available to or possessed by GSK, until 2018. Thus, it cannot serve as newly acquired information that would have triggered an obligation by GSK to unilaterally amend Zofran's label prior to 2018, at a time when GSK still owned the drug. Second, although Dr. Danielsson opines that the three Japanese animal studies at issue show evidence of teratogenicity, he also opines that the UK and Japanese studies submitted in 1990 by GSK also showed causation of birth defects, a conclusion that the FDA rejected in approving the original label. In short, Dr. Danielsson applied a standard not utilized by the FDA, and in doing so undercut any claim that the three Japanese studies at issue showed anything new. Third, to the extent that Dr. Danielsson's work can be read as advancing a type of meta-study in which two sets of insignificant findings become significant when combined, plaintiffs never made such an argument in the district court in opposing GSK's motion for summary judgment. Nor is it apparent that any such meta-study exists.[8]

[8] Dr. Danielsson's point is not so much that the addition of the Japanese animal studies would have alerted the FDA to new risks, but that the FDA should have been moved to act based on the risks raised by the other animal data it already had before it. We do not know whether it is Dr. Danielsson or the FDA that is correct on the science. Unfortunately for plaintiffs, it is not up to us to second-guess the FDA on such matters. See Celexa, 779 F.3d at 42-43.

To the extent plaintiffs now attempt to broaden their argument on this point, we treat it as forfeited. See Young v. Lepone, 305 F.3d 1, 13 (1st Cir. 2002) ("[L]egal theories not squarely raised in the lower court cannot be broached for the first time on appeal." (quoting Teamsters Union, Local No. 59 v. Superline Transp. Co., 953 F.2d 17, 21 (1st Cir. 1992))).[9]

Accordingly, we find that the three Japanese animal studies that form the basis of plaintiffs' contentions on appeal are not "newly acquired information" that would have enabled GSK to employ the CBE procedure.

B.

Our conclusion that plaintiffs' argument on appeal fails at its first step because there is no newly acquired information that would justify invoking the CBE procedure is sufficient to affirm the district court's ruling on alternative grounds. Nevertheless, we will address step two as well. The district court focused its analysis on that step, the parties have briefed it,

[9] Given the foregoing, we need not decide whether a plaintiff's expert report, presented in litigation, can qualify as "newly acquired information." Cf. In re Incretin-Based Therapies Prods. Liab. Litig., 524 F. Supp. 3d 1007, 1024–25 (S.D. Cal. 2021), aff'd, No. 21-55342, 2022 WL 898595 (9th Cir. Mar. 28, 2022) (doubting that a non-peer-reviewed "expert report [that] was generated in preparation for litigation" can constitute "newly acquired information"); R.S.B. v. Merck & Co., No. 20-civ-1402, 2021 WL 6128161, at *4 (E.D. Wis. Dec. 28, 2021) ("Plaintiffs are not entitled to create their own 'newly acquired information' through the use of experts.").

and we are cognizant of the fact that this appeal will bear on the disposition of many individual complaints in this multi-district litigation.

To review, the second step in plaintiffs' two-step argument goes as follows: Assuming that the Japanese animal studies not disclosed to the FDA in the initial approval process constituted newly acquired information with which GSK could have invoked the CBE procedure to change its label to state that animal studies showed teratogenic effects, GSK has failed to produce clear evidence that the FDA would have rejected such a change. Hence, compliance with both federal and state laws was not impossible.

To assess this argument, we begin by reciting the language in Albrecht and Wyeth upon which the parties train their dispute. In Wyeth, the Supreme Court stated that: "[A]bsent clear evidence that the FDA would not have approved a change to [the drug's] label, we will not conclude that it was impossible for [the manufacturer] to comply with both federal and state requirements." 555 U.S. at 571. In Albrecht, the Court explained what such "clear evidence" would entail "[i]n a case like Wyeth":[10]

[10] In Wyeth, there was no dispute whether the drug manufacturer possessed newly acquired information that would support a label change, and the Wyeth decision assumes that the manufacturer possessed such information. See Wyeth, 555 U.S. at 571 ("[W]hen the risk of gangrene from IV-push injection of Phenergan became apparent, Wyeth had a duty to provide a warning that adequately described that risk, and the CBE regulations permitted it to provide such a warning before receiving the FDA's

The manufacturer must show "that it fully informed the FDA of the justifications for the warning . . . and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." 139 S. Ct. at 1678. Albrecht also required that the FDA's disapproval must be the product of "agency action carrying the force of law." Id. at 1679.

As it applies to this case, we read Wyeth (as elaborated on by Albrecht) to require a defendant seeking to invoke preemption under the "clear evidence" prong to show that the FDA, after being fully informed of the case for making plaintiffs' proposed label change, made clear through agency action having the force of law that it would not have allowed the change had the defendant initiated it through the CBE procedure. Suffice it to say, such a demonstration is most easily made if the manufacturer actually initiates such a label change through the CBE procedure. But we find nothing in Wyeth or Albrecht to preclude other means of making the required showing.

Here, there is no doubt that by the time Novartis submitted the proposed updated label for Zofran in 2020, the FDA

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approval."). This case is not like Wyeth, because GSK disputes the existence of newly acquired information that would have supported a change to Zofran's label and, as explained earlier in this opinion, is entitled to a finding of preemption due to the lack of newly acquired information.

was fully informed of the Japanese studies. Indeed, the FDA was also fully informed of plaintiffs' contentions and the opinions of plaintiffs' experts. Some of this information was arguably supplied to the FDA by plaintiffs, not "the manufacturer." But we find the relevant issue to be whether the FDA was informed in a relevant context, not who exactly first informed it.[11] Nor was this an occasion on which it can be said that the FDA gave only "passing attention" to the label's statements concerning animal studies; both GSK and plaintiffs met with the FDA specifically on this issue. Cf. Wyeth, 555 U.S. at 572 (determining that the fact that neither "the FDA [n]or the manufacturer gave more than passing attention" to the risk against which plaintiffs sought a new warning undermined the manufacturer's assertion that the FDA would have prevented it from adding the requested warning).

So informed, the FDA approved the updated Zofran label. As plaintiffs concede, the "FDA's eventual 2021 approval of Novartis's revised label . . . is formal agency action with the force of law." That formal approval, in turn, applied to the entire label. And that approval meant that, absent subsequently acquired information, the manufacturer could not unilaterally change the label. 21 C.F.R. § 314.70(a)(1)(i), (c)(6)(iii).

[11] In any event, it is clear that GSK and Novartis ultimately gave the studies to the FDA.

The updated Zofran label that the FDA approved stated that animal data revealed "no significant effects of [Zofran] on the maternal animals or the development of the offspring." This language is fundamentally incompatible with plaintiffs' position that the label should state that the drug had been shown to be teratogenic in animal studies. We think it clear that when the FDA formally approves a statement that data reveals no effects, it necessarily rejects the contention that the data does reveal effects.

Albrecht reinforces this conclusion by teaching that "the meaning and scope of [agency action concerning a label] might depend on what information the FDA had before it." 139 S. Ct. at 1680. The record shows that the Japanese studies and plaintiffs' interpretation of those studies were not only before the agency, but also were prominently presented as cause for advancing plaintiffs' challenge to the pre-existing label. The fully informed FDA in approving the label stating "not-X" necessarily rejected plaintiffs' prominently presented case for stating "X." In so concluding, we need not opine that an agency's failure to sua sponte initiate a label change is equivalent to a determination that such a change is prohibited. We hold only that when the FDA formally approves a label stating one thing with full and obvious

notice of the directly contrary position, one can read the approval as rejecting the contrary position.[12]

IV.

For the foregoing reasons, we affirm the district court's grant of GSK's motion to dismiss.

[12] This is in line with Wyeth's conclusion that there was no clear evidence that the FDA would reject a label change where (i) newly acquired information existed and (ii) the record did not show either that the drug manufacturer informed the FDA of that information or that the FDA or manufacturer "gave more than passing attention" to the issue potentially supporting a label change. 555 U.S. at 572-73.