PUBLIC COPY – SEALED MATERIAL REDACTED

No. 21-1517

In the United States Court of Appeals for the First Circuit

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION

HEATHER PERHAM, et al,

Plaintiffs-Appellants,

v.

GLAXOSMITHKLINE LLC,

Defendant-Appellee,

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

Defendants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS (MDL NO. 1:15-MD-2657-FDS) (THE HONORABLE F. DENNIS SAYLOR IV)

BRIEF OF APPELLEE

SCOTT A. CHESIN
SHOOK, HARDY & BACON
2555 Grand Blvd
Kansas City, MO 64108
(816) 474-6660

LISA S. BLATT
AMY MASON SAHARIA
J. MATTHEW RICE
JAMI M. KING
WILLIAMS & CONNOLLY LLP
680 Maine Avenue, SW
Washington, DC 20024
(202) 434-5000

CORPORATE DISCLOSURE STATEMENT

GlaxoSmithKline LLC is a Delaware limited liability company whose sole member is GlaxoSmithKline Holdings (Americas) Inc., a Delaware corporation with its principal place of business in Wilmington, Delaware. GlaxoSmithKline LLC is an indirect, wholly owned subsidiary of GSK plc (f.k.a. GlaxoSmithKline plc), a publicly traded company organized under the laws of England. GSK plc Ordinary Shares are traded on the London Stock Exchange and in the form of American Depositary Receipts on the New York Stock Exchange.

To the knowledge of GlaxoSmithKline LLC, none of the shareholders of GSK plc owns beneficially 10% or more of its outstanding shares. However, JP Morgan Chase Bank, N.A. (JPM) acts as Depositary in respect for the GSK plc's American Depositary Shares listed on the New York Stock Exchange, each representing two Ordinary Shares in GSK plc. In that capacity, JPM is the legal holder of more than 10% of the outstanding shares in GSK plc.

/s/ *Lisa S. Blatt*
LISA S. BLATT
WILLIAMS & CONNOLLY LLP
680 Maine Avenue, SW
Washington, DC 20024
(202) 434-5000

(202) 434-5029 (fax)
lblatt@wc.com

DATED: May 16, 2022

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page

CASES

Page

Cases—continued:

STATUTES, REGULATIONS, AND RULE

OTHER AUTHORITIES

Page

Other authorities—continued:

INTRODUCTION

This case presents an open-and-shut case for preemption, as the district court's comprehensive decision granting judgment in favor of GlaxoSmithKline LLC (GSK) reflects. GSK has provided the Food and Drug Administration (FDA) a broad array of information concerning the safety of Zofran, including epidemiological and animal data. With that information, FDA has rejected, in 2015, 2016, and 2021, proposals to add enhanced warnings against use of Zofran during pregnancy. The agency has consistently taken the position that (1) the evidence does not demonstrate an association between Zofran and birth defects and (2) the warnings that Plaintiffs urge would mislead patients. To this day, Zofran's labeling—which FDA reapproved just last year—does not warn that Zofran causes or even *might* cause birth defects.

Disagreeing with FDA's conclusion, Plaintiffs claim that use of Zofran in pregnancy causes birth defects. Given FDA's consistent refusal to warn against use of Zofran in pregnancy, however, it was impossible for GSK to add the warnings that Plaintiffs claim state law required. In an attempt to stave off preemption, Plaintiffs scoured the record below for any data that FDA allegedly did not have when it first rejected enhanced warnings in 2015 and 2016.

They identified certain animal studies that GSK sponsored in Japan to obtain regulatory approval in that country and that GSK identified to FDA three decades ago. Although the Japanese study investigators found *no* evidence that Zofran causes birth defects—conclusions echoed in peer-reviewed published articles in Japan—Plaintiffs produced in litigation an expert opinion reinterpreting the studies to show the opposite. If only FDA had considered the studies, Plaintiffs claimed, the agency supposedly would have allowed GSK to revise the labeling to include an enhanced pregnancy warning.

That argument was flawed from the start: FDA did review one of GSK's Japanese animal studies in 1997 and concluded—contrary to the opinion of Plaintiffs' expert—that the study did not show that Zofran causes birth defects. Recent events made that argument all the more untenable. In 2019 and 2020, GSK and *Plaintiffs themselves* presented their views on all the Japanese animal studies directly to FDA, providing the agency with the translated studies, PowerPoint presentations on the studies, and even Plaintiffs' expert reports discussing the studies. Plaintiffs omit these critical presentations from their brief on appeal. Armed with this information, FDA nonetheless found no association between Zofran and birth defects and rejected a third request for an enhanced pregnancy warning—making abundantly clear that

"FDA would not have approved" the warning that Plaintiffs claim state law required. *Wyeth v. Levine*, 555 U.S. 555, 571 (2009).

FDA's unwavering position is entirely unsurprising, because the Japanese animal studies are not the kind of evidence that would have permitted GSK to change Zofran's labeling. Only "newly acquired information" providing "evidence of a causal association" between a drug and a hazard permits a manufacturer to change a drug's labeling. 21 C.F.R. § 314.70(c)(6)(iii)(A). The investigators who conducted the Japanese studies concluded that the small numbers of observed birth defects fell within expected background rates and that the studies revealed no evidence that Zofran causes birth defects—another critical fact that Plaintiffs omit from their brief. The Japanese studies revealed no risks that differed from those in the United Kingdom studies submitted with GSK's original application. That is undoubtedly why FDA rejected enhanced warnings yet again, even after hearing Plaintiffs' arguments on the Japanese studies. In FDA's considered scientific judgment, [redacted] SJA-1790. Plaintiffs cannot defeat preemption by asking this Court to second-guess that judgment.

If preemption is not warranted on this record—where all material information was not only before FDA, but Plaintiffs themselves directly argued their causation theory to the agency—then preemption would *never* be warranted. This Court should affirm the district court's straightforward application of the *Wyeth* preemption inquiry.

STATEMENT OF THE ISSUES

I. Whether the district court correctly held that federal law preempts Plaintiffs' claims under the second step of *Wyeth* where FDA, after considering the scientific data, has repeatedly rejected proposals for an enhanced warning.

II. Whether, alternatively, federal law preempts Plaintiffs' claims under the first step of *Wyeth* because the Japanese animal studies were not "newly acquired information" providing "evidence of a causal association" between Zofran and birth defects.

STATEMENT OF THE CASE

A. Statutory and Regulatory Framework

1. The Federal Food, Drug, and Cosmetic Act bars drug companies from marketing or selling new pharmaceutical products without FDA's approval. 21 U.S.C. § 355(a). To obtain approval, a drug manufacturer (the sponsor) submits a New Drug Application (NDA) for FDA's review. *See id.*

"The process of submitting an NDA is both onerous and lengthy." *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013). Manufacturers must provide substantial information about the drug, including scientific data about its safety and efficacy and the proposed labeling. 21 U.S.C. § 355(b)(1); 21 C.F.R. §§ 314.50(d)(5)(viii), 201.57(a). FDA will approve a drug for marketing only if the NDA demonstrates that the drug is "safe for use," "will have the effect it purports or is represented to have," and contains labeling that is neither "false [n]or misleading in any particular." 21 U.S.C. § 355(b)(1)(A), (d).

FDA regulations govern the format and substance of drug labeling. *See, e.g.*, 21 C.F.R. §§ 201.56, 201.57; *see id.* § 201.100(c). The agency conducts "a detailed review of the proposed labeling." 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008); *see* 21 U.S.C. § 355; 21 C.F.R. § 314.105(c). The agency "allow[s] only information for which there is a scientific basis to be included in the FDA-approved labeling." 73 Fed. Reg. at 49,604. In FDA's considered judgment, warnings about scientifically unsupported risks harm patients: "Exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug" and "cause meaningful risk information to lose its significance." 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008); *see also Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1102 (10th Cir. 2017). FDA thus "makes careful

judgments about what warnings should appear on a drug's label for the safety of consumers." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1672 (2019).

2. The statutory and regulatory framework allows drug manufacturers, private citizens, and FDA to make, request, or order labeling changes through defined processes.

Manufacturers "generally seek advance permission from the FDA to make substantive changes to their drug labels" by submitting a Prior Approval Supplement, or "PAS." *Albrecht*, 139 S. Ct. at 1673; *see also* 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). This process resembles the process for obtaining initial approval for a drug's labeling. FDA "follows many of the general principles applicable to its review of an NDA when undertaking the more limited task of reviewing supplements that propose safety-related labeling changes." Brief for U.S. at 5, *Albrecht* (No. 17-290), 2018 WL 4562163 ("*Albrecht* Br."). Among other things, FDA "communicate[s] with applicants about scientific, medical, and procedural issues that arise during the review process," 21 C.F.R. § 314.102(a), and "exercise[s] its scientific judgment" in analyzing the data presented in the PAS, *id.* § 314.105(c).

In narrow circumstances, manufacturers may unilaterally amend labeling through the Changes Being Effected (CBE) regulation and seek after-the-fact FDA approval. The CBE process permits manufacturers to "add or strengthen" a warning where "newly acquired information" provides "evidence of a causal association" between the drug and a significant hazard. 21 C.F.R. §§ 314.70(c)(6)(iii)(A), 201.57(c)(6)(i); *see also* 73 Fed. Reg. 2851. To constitute "newly acquired information," information must "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). FDA approves revisions made through the CBE process only if they satisfy the regulatory criteria. 21 C.F.R. § 201.70(c)(6), (7); *see Albrecht*, 139 S. Ct. at 1679. If the agency finds no "newly acquired information" or insufficient evidence of a causal association, the agency may order the manufacturer to stop distributing drugs with the revised labeling. 21 C.F.R. § 314.70(c)(7). The CBE process is "intended to ensure that scientifically valid and appropriately worded warnings will be provided in the approved labeling for medical products, and to prevent overwarning." 73 Fed. Reg. at 49,605.

FDA also allows private individuals and organizations to request changes to a drug's labeling by filing a citizen petition requesting that FDA

"issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action." 21 C.F.R. § 10.30(b)(3). In reviewing such requests, FDA applies the same "standard . . . regardless of who proposes to revise the label." *Cerveny*, 855 F.3d at 1102.

Finally, FDA has authority to *require* changes to an approved drug's labeling under the agency's statutory duty to ensure that labeling contains complete, accurate, and up-to-date information. Federal law requires FDA to "promptly notify" the manufacturer if it "becomes aware of new safety information" that it "determines should be included in the labeling of the drug." 21 U.S.C. § 355(*o*)(4)(A). The manufacturer must then submit a supplement including the changes ordered by FDA or otherwise engage with FDA to reach agreement on the labeling. 21 U.S.C. § 355(*o*)(4)(B), (C).

B. Factual Background

1. Zofran and its labeling

In 1991, FDA approved the marketing and sale of ondansetron hydrochloride—better known as Zofran—to treat nausea and vomiting associated with chemotherapy. JA-1068, 1076.[1] Zofran revolutionized the treatment of

[1] "JA" refers to the publicly filed joint appendix. "SJA" refers to the sealed supplemental appendix.

chemotherapy patients, reducing nausea and increasing patient acceptance of potentially life-saving treatments. JA-2684-90. It was later approved to treat radiation-related and post-surgical nausea and vomiting. JA-1190. Zofran remains on the market, and to this day its FDA-approved labeling does not suggest any association between Zofran and birth defects.[2]

Birth defects occur spontaneously in nature, in both humans and animals. According to FDA, "[t]he background incidence of major congenital anomalies [in humans] is 2-4%," and "cardiac malformations . . . affect nearly 1% of births per year in the US." JA-1352, 1367. Accordingly, as a matter of "chance alone," some malformations will occur in fetuses whose mothers consume Zofran. JA-1367.

As part of Zofran's approval process, GSK submitted to FDA data relating to Zofran's safety and efficacy during pregnancy, including four animal reproductive studies conducted on rats and rabbits in the United Kingdom (U.K.). JA-2286, 5651-932, 6376-779. The investigators observed a handful of birth defects during these studies, as would be expected given the natural rate

[2] Like all drugs, Zofran can cause certain adverse reactions in a small number of patients. Plaintiffs describe some of those potential reactions (at 6), without mentioning that Zofran's labeling warns about those reactions. *See, e.g.*, JA-11027 (QT prolongation, Torsade de Pointes, and serotonin syndrome).

of spontaneous occurrence of such defects. But the investigators uniformly found no evidence of a causal association between Zofran and birth defects. JA-5664, 5670, 5875, 5885, 6377, 6382, 6546-49. FDA itself reviewed the U.K. animal studies and agreed in its internal Pharmacology Review that "ondansetron . . . did not induce any teratogenic effect."[3] JA-2338; *see also* JA-2336, 2340, 2337.

To obtain approval of Zofran in Japan, GSK sponsored rat and rabbit studies in Japan. JA-3982-4972. These studies paralleled the U.K. studies, using the same animal (rats and rabbits), same formulation (oral or intravenous (IV)), and same method of selecting dosages. *See generally* JA-4973-5036, 5611-974, 6376-789 (U.K. studies); JA-3982-4972 (Japanese studies). Like the U.K. studies, the Japanese studies reported only a handful of adverse outcomes that fell well within the expected rates of spontaneous birth defects. *E.g.*, JA-4083 n.7, 4390 n.7; *see* JA-2846-60. And like the U.K. investigators and FDA, the Japanese investigators concluded that Zofran "was considered to have no teratogenicity." JA-4083, 4390, 4784. Peer-reviewed publications

[3] A "teratogenic" drug is one that causes birth defects when consumed during pregnancy.

in Japan reaffirmed these conclusions. JA-7647-786. Zofran was approved for use in Japan.

At the time of Zofran's FDA approval in 1992, FDA's regulations classified drugs into five categories of safety for use during pregnancy (A, B, C, D, or X), and each category had standardized pregnancy-warning language. 21 C.F.R. § 201.57(f)(6)(i) (1991). Because toxicity studies "failed to demonstrate a risk to the fetus and there [were] no adequate and well-controlled studies in pregnant women," *id.* § 201.57(f)(6)(i)(b), FDA assigned Zofran a Category B designation. Zofran's original labeling thus stated:

> Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at intravenous doses up to 4 mg/kg per day (approximately 1.4 and 2.9 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, respectively, based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. 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.

JA-1118. The next designation, Category C, would have been warranted when animal studies showed a drug "to be teratogenic (or to have an embryocidal effect or other adverse effect)." 21 C.F.R. § 201.57(c)(6)(i)(c) (1991).

Shortly after Zofran's approval, GSK's December 1993 annual report described the Japanese animal studies, listing the studies by name and number (as required by FDA regulations). *See* JA-3873; 21 C.F.R § 312.33 (1993). The report stated that the studies were "performed specifically to satisfy Japanese regulatory requirements," and were "repetitive and provide[d] no new safety information." JA-3872.

FDA ultimately approved four additional NDAs for varying Zofran formulations: oral tablet (1992); premixed injection (1995); oral solution (1997); and orally disintegrating tablet (1999). JA-1068-82, 1110-38. FDA assigned the Category B designation to each formulation. JA-1077, 1127.

In 1997, in connection with its NDA for Zofran's oral solution, GSK submitted to FDA a translated version of one of the Japanese studies, Study No. 100422. JA-446-47, 2548. After reviewing the study, FDA stated in its internal Pharmacology Review that the "results [of No. 100422] are comparable to those for [the U.K. counterpart study] included in the original submissions," JA-2552, and that Zofran "was not teratogenic," JA-2548. Plaintiffs mention GSK's 1997 submission of Study No. 100422 in a footnote (at 12 n.5), but do not mention FDA's conclusion after reviewing the study.

2. FDA's rejections of enhanced warnings

1. *FDA's 2011 pregnancy review*: Nausea and vomiting in pregnancy affects many women. JA-1190. Its most severe form, known as hyperemesis gravidarum, afflicts up to 2% of pregnant women and can threaten the health of women and their fetuses and require hospitalization. *Id.* For many years, the market lacked a drug approved by FDA to treat hyperemesis gravidarum and other pregnancy-related nausea and vomiting. As a result, doctors have long prescribed Zofran off-label to treat pregnancy-related nausea and vomiting.[4]

In 2010, prompted by information that pregnant women commonly use Zofran off-label, FDA asked GSK to "review and analyze available published and unpublished literature on the use of ondansetron during pregnancy" and to provide "an assessment of the strengths and limitations of the data." JA-1140. If labeling changes were necessary to "furnish adequate information for the safe use of this drug," the agency stated, GSK should propose such revisions through a prior approval supplement (PAS). *Id.*

[4] "[T]he prescription of drugs for unapproved uses is commonplace in modern medical practice and ubiquitous in certain specialties." *Wash. Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000).

GSK responded with a detailed examination of Zofran's safety data in 2011, *see* JA-1144-67, and advised FDA that it did "not believe there [wa]s sufficient evidence to warrant a change in [Zofran's labeling]," JA-1160-61.

2. *FDA's denial of 2013 citizen petition*: In 2013, James Reichmann submitted a citizen petition asking FDA to revise the Zofran pregnancy-related labeling to reclassify Zofran—from Category B to Category C, D, or X—and to warn doctors that use of Zofran during pregnancy may lead to "adverse maternal and/or fetal outcomes." JA-1174-79. In October 2015, FDA denied the petition in a 20-page letter. JA-1188-207. FDA concluded that "the totality of the data do not support a conclusion that there is an increased risk of fetal adverse outcomes . . . among fetuses exposed to ondansetron." JA-1205. Accordingly, FDA declined to change Zofran's labeling, stating that "pregnancy category B was the appropriate risk category for ondansetron when it was assigned and . . . remains appropriate today." JA-1205. FDA also declined to warn that use of Zofran during pregnancy increases the risk of adverse outcomes. JA-1206-07. Such a warning, FDA explained, "could be misleading" because "the available data do not support a conclusion that there are increased safety risks . . . for the fetus." JA-1206; *see* Add. 14-15.

3. FDA's *rejection of Novartis's 2016 proposed labeling change*: In December 2014, FDA changed the pregnancy warning requirements for all drugs. *See* Pregnancy and Lactation Labeling Rule (PLLR), 79 Fed. Reg. 72,064 (Dec. 4, 2014). The Rule eliminated the pregnancy categories and, instead, required drug manufacturers to provide labeling addressing pregnancy-related risks and benefits in narrative form. *Id.* A drug's labeling must contain a risk statement summarizing the animal (*i.e.*, pre-clinical) data and human (*i.e.*, epidemiological or clinical) data under the heading "Risk Summary." *Id.* The rule also requires distinct subsections describing the animal and human data. *Id.*

In early 2015, Novartis acquired Zofran from GSK and, as Zofran's new sponsor, assumed responsibility for conforming Zofran's labeling to the PLLR. JA-506-08. At the same time, and as discussed below, Plaintiffs were beginning to file lawsuits claiming that Zofran's labeling failed to warn against the risk of using Zofran in pregnancy. Novartis's proposed labeling, submitted to FDA in September 2015, included several warnings against use of Zofran in pregnancy. JA-1209-39. Novartis accompanied its proposed revisions with [redacted]

[redacted] SJA-133-179; *see* Br. 39-40 & n.15. Novartis expressed its view that, [redacted] SJA-172.

FDA rejected Novartis's proposed enhanced warnings. JA-1242-65. For example, in the "Risk Summary" section, Novartis proposed adding a statement that "[a]nimal studies are not always predictive of human response, therefore, the use of ondansetron in pregnancy is not recommended," but FDA did "not agree with keeping this statement in labeling." JA-1250. Novartis also proposed creating a new subsection entitled "Females and males of reproductive potential," stating in part: "Advise females of reproductive potential that it is possible that ZOFRAN can cause harm to the developing fetus." JA-1252. FDA likewise rejected that proposal. *Id.*

Novartis and FDA then engaged in several rounds of communications. First, in December 2015, Novartis submitted a new round of proposed labeling. JA-1267-91. And, in April 2016, FDA again rejected Novartis's proposals.

JA-1293-320. For instance, Novartis proposed that the Adverse Reactions section state that "[c]ases of congenital malformations have been reported in infants whose mothers took ondansetron during pregnancy." JA-1274. But FDA demurred, concluding that there was no "basis to believe there is a causal relationship between the congenital malformations and the use of ondansetron." JA-1301. Novartis also proposed that the Risk Summary warn that "[t]he safety of ondansetron for use in human pregnancy has not been established." JA-1275. FDA deleted that language. JA-1302.

Following FDA's April 2016 revisions, Novartis and FDA engaged in two more rounds of edits before reaching the final labeling. JA-1322-42, 1344-67, 1369-89. During these communications, FDA explained that there "is no evidence, nonclinical [*i.e.*, animal] or mechanism of action, that raises concerns for adverse fetal outcomes with Zofran." JA-1353. FDA further explained that warning about such a risk "could be misleading in implying that FDA has some concerns about the role of Zofran in a variety of fetal malformations." *Id.*; *see* Add. 15-18.

The labeling that FDA approved in 2016 advised that "[a]vailable data do not reliably inform the association of ZOFRAN and adverse fetal outcomes." JA-1376. The labeling also informed doctors that animal study data

do not show any significant effects on fetal development other than a slight decrease in maternal body weight for rabbits. JA-1377.

4. *GSK's 2019 citizen petition*: Notwithstanding Plaintiffs' claim that Zofran's labeling failed to warn against the risk of birth defects, Plaintiffs have never asked FDA to change the labeling. In November 2019, GSK itself submitted a citizen petition to FDA. JA-7983-8000. Identifying this pending litigation, the petition asked FDA to review four categories of information concerning Zofran's use in pregnancy that Plaintiffs alleged GSK had omitted in its prior FDA submissions, including, as relevant here, the data underlying three of the Japanese animal studies identified in GSK's 1993 annual report. JA-7984, 7989-94. (Plaintiffs have abandoned their claims based on the other three categories. *See* Br. 19 n.9.[5]) GSK requested that FDA "either refrain

[5] Plaintiffs' other three categories were (1) a description of Dr. Danielsson's theory of Zofran's "biological mechanism of action," (2) allegedly miscoded adverse event data, and (3) information concerning GSK's involvement in, and assessment of the limited value of, the so-called Einarson birth defect study. Add. 29. But GSK promptly disclosed to FDA Dr. Danielsson's 2014 article setting forth his hERG-blocking "mechanism of action theory," and FDA discussed that article when it rejected the Reichmann citizen petition in 2015. Add. 36. FDA nonetheless told Novartis in 2016 that it saw no "mechanism of action" evidence "that raises concerns for adverse fetal outcomes with Zofran." JA-1353. Both GSK and Novartis regularly supplied FDA with adverse event data and analyses, and no evidence showed that the specific analyses that Plaintiffs claimed were miscoded were even shared with FDA. Add. 40-41. And the Einarson publication disclosed GSK's funding, and FDA

from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling in light of these four categories of information." JA-7984; *see* 21 C.F.R. § 10.30(b)(3) (citizen petition may ask FDA to "take or refrain from taking" administrative action). GSK attached 59 exhibits—including the translated Japanese animal studies. JA-7997-8005. GSK's petition also noted GSK's understanding that FDA would soon review Zofran's safety profile, together with Novartis, "as a result of newly available epidemiological studies." JA-7984.

Plaintiffs asked FDA to dismiss the petition. JA-9671. Plaintiffs stated that "the issue that is *actually* relevant to the agency [is] whether Zofran should carry a stronger 'use-during-pregnancy' warning based on *all* of the best available scientific information today." JA-9672 (second emphasis added).

FDA subsequently invited both GSK and Plaintiffs to meet with FDA. JA-9703-04. On March 5, 2020, GSK representatives presented to FDA a PowerPoint addressing the four categories of information. JA-9709-47. On March 30, 2020, Plaintiffs' counsel presented a PowerPoint to FDA. JA-9764-823; *see also* JA-9752-62, 9825-31. Both parties' presentations contained detailed

---

itself acknowledged when it denied the Reichmann petition that the Einarson study "was of limited size and statistical power." Add. 41-42.

slides on the Japanese studies. *See, e.g.*, JA-9716-24; JA-9764-70, 9785-94. Following the presentations, Plaintiffs submitted to FDA *an additional 30 documents*, including reports from Plaintiffs' experts—Dr. Danielsson and Dr. Harvey—discussing the Japanese studies. JA-9833-34. Before FDA could resolve GSK's petition, Novartis submitted a PAS proposing to revise Zofran's labeling. *See infra* pp. 21-25.

On January 15, 2021, FDA denied GSK's petition. JA-10468-83. FDA stated that it was declining to assess whether—"separate and apart from FDA's ongoing product review" with Novartis, JA-10469—the four categories of information "in isolation" warranted a labeling change. JA-10482. FDA did so because the agency "evaluates whether safety-related labeling changes are warranted based on the review of *all* relevant information available to the Agency." JA-10469.

FDA discussed at length "the depth of FDA's engagement in the scientific evaluation of relevant data and information in determining the safety-related information that should be included in FDA-approved labeling." JA-10469. FDA noted that it had long been "aware of the unapproved use of ondansetron" to treat nausea and vomiting in pregnancy. JA-10480. FDA also highlighted its active assessment of data to fulfill its obligation to determine

whether "new information, including any new safety information . . . , should be included in the labeling of the drug." JA-10479 (cleaned up) (quoting 21 U.S.C. § 355(*o*)(4)(A)). FDA explained that its "evaluation" of "proposed labeling changes" (such as those in Novartis's pending PAS) "requires the review of *all* relevant information before the Agency." JA-10482. FDA observed that the labeling describes "data from reproductive studies in rats and rabbits" and that the Risk Summary "explains that those studies did not show evidence of harm to the fetus." JA-10481. In concluding, FDA stated its intent to "continue to monitor and review available safety information related to ondansetron products" and "take further action if . . . it is appropriate to do so." JA-10483; *see* Add. 18-22.

5. *FDA's rejection of Novartis's 2020 PAS*: [redacted] SJA-1661. [redacted]. SJA-1661-62. [redacted] SJA-1697. [redacted]

[redacted] SJA-1696. [redacted]

[redacted] SJA-1697. [redacted]

[redacted] *see* SJA-1777) [redacted]

[redacted] SJA-1697. [redacted]

[redacted] SJA-1713. [redacted]

[redacted] SJA-1674-75. [redacted]

SJA-1717-42, 1744-68, 1770-78; *see* JA-9359-70, 9413-565.[6]

[6] Dr. Danielsson's paper was based in part on Study No. 100422, which, as discussed above, FDA reviewed in 1997 and concluded that it showed no evidence of teratogenicity. *See supra* pp. 12, 62.

[redacted] SJA-1674. [redacted] SJA-1713. [redacted] SJA-1674.

[redacted] SJA-1676.

[redacted] *see* SJA-1780-99: [redacted] SJA-1789; [redacted] SJA-1790.

[redacted] SJA-1789, [redacted] SJA-1790. [redacted] SJA-1788. [redacted] SJA-1790. [redacted] *Id.* [redacted] SJA-1814. [redacted]

[redacted]

SJA-2232.[7]

[redacted] SJA-2250-92. FDA then approved the revised Zofran labeling with a final change: FDA added the word "oral" to one sentence in the animal data subsection to clarify how rats in a certain study received Zofran. JA-11019, 11031. The final approved labeling continues to report in the Risk Summary that "[r]eproductive studies in rats and rabbits did not show evidence of harm to the fetus." *E.g.*, JA-11030; *see* Add. 22-29.

C. Procedural History

In 2015, while Reichmann's citizen petition was pending, a number of plaintiffs filed suit against GSK, alleging that use of Zofran during pregnancy caused various birth defects. Although Plaintiffs pleaded various state-law

---

[7] [redacted] SJA-1814-15. The district court found below that Dr. Zambelli-Weiner, Plaintiffs' consulting expert, "made false statements to the Court [in an affidavit] as to the nature of her relationship with plaintiffs' counsel" in this case. JA-7266. [redacted] SJA-1707, 1814-15, [redacted] SJA-2220.

tort theories, they generally claimed that GSK failed to provide adequate warnings of the risks of ingesting Zofran during pregnancy. JA-183-258. Plaintiffs alleged that GSK should have warned that "the use of ondansetron in pregnancy is not recommended." JA-197 (¶ 52). The Judicial Panel on Multidistrict Litigation created a coordinated MDL proceeding.

1. GSK moved for summary judgment, arguing that federal law preempts Plaintiffs' state-law failure-to-warn claims under *Wyeth v. Levine*, 555 U.S. 555 (2009). GSK argued that, given FDA's rejections of enhanced pregnancy warnings in its 2015 denial of the Reichmann citizen petition and its 2016 action on Novartis's PAS, federal law prevented GSK from unilaterally changing Zofran's labeling to add the warning allegedly required by state law. In an attempt to avoid preemption, Plaintiffs contended that GSK had failed to disclose to FDA four categories of evidence, including three Japanese animal studies, foreclosing preemption. In February 2019, the court denied GSK's motion, concluding that preemption raised a fact issue for a jury. JA-354, 387.

2. After the court's decision, the law and facts underlying the preemption inquiry evolved. First, on May 20, 2019, in *Albrecht*, the Supreme Court held that *Wyeth* preemption must be treated "not as a matter of fact for

a jury but as a matter of law for the judge to decide." 139 S. Ct. at 1679. On July 16, 2019, the court vacated its prior decision in relevant part and authorized GSK to renew its motion for summary judgment in light of *Albrecht*. JA-421-22.

Second, while GSK's renewed motion was pending, GSK filed its 2019 citizen petition, Novartis submitted its 2020 PAS, FDA denied GSK's citizen petition, and FDA acted on Novartis's PAS, as discussed above. *See supra* pp. 18-25. The parties discussed these developments in real time with the district court at monthly status conferences, *see, e.g.*, JA-11354 (Nov. 5, 2019), 11434 (Nov. 20, 2019), 11563 (Apr. 15, 2020), 11605 (July 22, 2020), 11697 (Nov. 16, 2020), 11814 (Jan. 22, 2021), and submitted supplemental briefing to the court in late 2020. The court itself corresponded with FDA to urge FDA to resolve the citizen petition as expeditiously as possible. JA-7846-49, 9699. In so doing, the court explained that Plaintiffs claimed that "GSK improperly withheld certain information from the FDA concerning the dangers of ingesting Zofran during pregnancy," and that GSK contended that the exhibits to its citizen petition "included all the information that plaintiffs allege was wrongfully withheld." JA-7847-48.

3. In June 2021, the court granted judgment to GSK in a 68-page opinion, holding that federal law preempts Plaintiffs' state-law claims. Add. 1-68. The court assumed, without deciding, that Plaintiffs were correct that four categories of evidence "constituted 'newly acquired information' as defined by the CBE regulations, and that therefore GSK could have attempted to amend the Zofran label unilaterally" under the CBE process. Add. 54. But the court nonetheless found Plaintiffs' claims preempted because "clear evidence" shows that "FDA would not approve changing the Zofran label to include the warning that plaintiffs contend is required by state law." Add. 62; *see* Add. 58-63. The court explained that "[FDA] has effectively rejected those changes, and indeed approved contrary language." Add. 6.

The court observed that "FDA rejected enhanced pregnancy warnings when it rejected the 2013 Reichmann citizen petition and when it rejected Novartis's proposed warnings in its 2015 PAS." Add. 62. The court stated that "all of the information concerning the safety of Zofran that plaintiffs allege was withheld from the FDA [at the time of those prior actions] had been provided to it by the time of the 2020 Novartis PAS." Add. 57. Then, "in 2021, after having considered the very evidence that plaintiffs contend requires an enhanced warning—indeed, after reviewing plaintiffs' evidence and plaintiffs'

expert reports—the FDA [again rejected enhanced warnings.]" Add. 62-63. "Preemption does not require a fourth attempt," the court concluded. Add. 63.

The court addressed, and rejected, Plaintiffs' argument that FDA's rejection of the 2020 Novartis PAS lacked preemptive effect because Novartis only requested "generalized safety warnings or warnings related to human epidemiological studies" but not "warnings related to animal studies." Add. 60 (emphasis omitted). The court observed that Novartis, GSK, and Plaintiffs each asked FDA to consider the animal data. Add. 60. The court noted that FDA had explained that the labeling must "describe for the drug the risk of adverse development outcomes based on *all* relevant human data, animal data, and/or the drug's pharmacology." Add. 61 n.31. And the court found it implausible that, in revising Zofran's labeling, FDA "turned a blind eye to evidence that Zofran causes birth defects" simply because Novartis had not requested "the precise warning" that Plaintiffs urged. Add. 61-62 (citing cases). In short, the court held there was "little doubt that the FDA would not approve the label that plaintiffs say is required by state law." Add. 63.

4. GSK's *Daubert* motions to exclude the opinions of Plaintiffs' causation experts—opinions that contradict FDA's conclusion that no evidence shows an association between Zofran and birth defects—remained pending

when the district court granted judgment on preemption grounds. Plaintiffs' own epidemiology expert, Dr. Carol Louik, agrees in large part with FDA. In a game-changing admission at her October 2020 deposition, Dr. Louik stated that, after reviewing all epidemiological and non-human data, she could not opine that even an association—much less a causal association—exists between Zofran and cardiac defects. *See* JA-10381-82, 10384-87, 10395-97, 10437, 10443-45.[8]

SUMMARY OF ARGUMENT

Federal law prohibited GSK from unilaterally adding warnings that FDA has three times found unwarranted and misleading. Initially, Plaintiffs argued below that FDA's rejections in 2015 and 2016 lacked preemptive effect because FDA did not have three Japanese animal studies when it rejected enhanced pregnancy warnings. That argument was always doomed to fail: the studies themselves found no association between Zofran and birth defects, and they merely duplicated the U.K. studies and Japanese Study No. 100422 known to FDA—same animals, same formulations, and same conclusions.

[8] GSK's motion for summary judgment in all cases alleging cardiac defects, which was based on lack of admissible expert evidence, was also pending.

Plaintiffs' preemption argument fell apart for good, though, when FDA rejected enhanced pregnancy warnings for a third time with full knowledge of the Japanese studies—indeed, after hearing arguments about the studies from Plaintiffs' counsel themselves.

I. The district court correctly ruled that FDA's recent action on Novartis's 2020 PAS requires preemption at *Wyeth* step two. FDA's action provides clear evidence that FDA would not approve the Category C warning that Plaintiffs claim state law requires, *i.e.*, that Zofran "has been shown to be teratogenic" or that "animal studies showed harm to the fetus." Br. 8; *see also* Br. 2, 28. The agency knew everything there was to know about the Japanese studies: FDA possessed the translated studies, had Plaintiffs' expert reports, and even heard a presentation from Plaintiffs' counsel about the studies. [redacted] SJA-1789-90. FDA then reaffirmed the labeling's statement that the animal data "did not show evidence of harm to the fetus." JA-11030. On this record, Plaintiffs' claim that GSK could have warned that Zofran *does* cause harm to the fetus is fanciful.

Plaintiffs urge the Court to hold that FDA action preempts state-law claims only when FDA expressly states that it considered and rejected the verbatim warning advocated by plaintiffs—here, that animal studies prove that Zofran causes birth defects. The scope and effect of FDA action, however, turn on the information *available to* FDA and FDA's actions based on that information—not on whether FDA utters magic words that provide proof of its internal considerations. In any event, given FDA's unparalleled attention to the issues presented by this case, it is implausible that FDA failed to consider the animal studies, as the district court correctly found. Nor does the law require FDA to reject Plaintiffs' desired warnings word for word. FDA's action on the Novartis PAS rejected the *substance* of Plaintiffs' desired warnings—that Zofran causes birth defects—with full knowledge of the Japanese studies. Preemption is required.

FDA's 2015 and 2016 actions independently require preemption at *Wyeth* step two. Both provide clear evidence that FDA would not approve the warnings Plaintiffs desire; indeed, FDA expressly rejected a Category C warning. And FDA was fully informed of all material information when it took

those actions: GSK had disclosed the existence of the Japanese studies in compliance with FDA's regulations and had accurately told FDA that the studies did not provide new safety information.

II. Alternatively, the Court should affirm because GSK is also entitled to preemption at *Wyeth* step one. That step asks whether the manufacturer possessed "newly acquired information" providing "evidence of a causal association" between a drug and a hazard that would permit a manufacturer to use the CBE process to change the labeling. *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1673 (2019) (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)); *see also* 21 C.F.R. § 201.57(c)(6)(i). The three Japanese studies that Plaintiffs invoke are neither "newly acquired information" nor "evidence of a causal association."

"Newly acquired information" must "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). Plaintiffs identify no evidence that the three Japanese studies revealed risks different, more severe, or more frequent than risks revealed in previous submissions to FDA; none of their experts so opined. And FDA's recent action unassailably proves that the studies do not prove the requisite "causal association" between Zofran and birth defects. 21

C.F.R. §§ 201.57(c)(6)(i), 314.70(c)(6)(iii). FDA itself said that the evidence does not prove a causal association in rejecting Novartis's proposed warnings.

STANDARD OF REVIEW

This Court reviews an order granting summary judgment de novo. *Houlton Citizens' Coal. v. Town of Houlton*, 175 F.3d 178, 184 (1st Cir. 1999). A federal preemption determination presents a legal question subject to plenary review. *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1679-80 (2019); *United States v. R.I. Insurers' Insolvency Fund*, 80 F.3d 616, 619 (1st Cir. 1996).

In analyzing preemption, district courts "'may have to resolve subsidiary factual disputes' that are part and parcel of the broader legal question." *Albrecht*, 139 S. Ct. at 1680 (quoting *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 327 (2015)). Rule 52(a) of the Federal Rules of Civil Procedure "requires appellate courts to review all such subsidiary factual findings under the 'clearly erroneous' standard." *Teva Pharms.*, 574 U.S. at 327; *Albrecht*, 139 S. Ct. at 1680 (citing *Teva* and drawing parallel between preemption and construction of patent claims); *see also Hillsborough Cnty. v. Automated Med. Lab'ys*, 471 U.S. 707, 720-21 (1985) (reviewing preemption-related factual findings for clear error). A finding is "clearly erroneous" when the reviewing court

"is left with the definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948). If a factual determination appears "plausible in light of the record viewed in its entirety," this Court "may not reverse it even [if the Court were] convinced that had it been sitting as the trier of fact, it would have weighed the evidence differently." *Anderson v. Bessemer City*, 470 U.S. 564, 573-74 (1985).

ARGUMENT

Federal law preempts state law when it is not possible "for a private party to comply with both state and federal requirements." *Albrecht*, 139 S. Ct. at 1672. In other words, "where state and federal law directly conflict, state law must give way." *Wos v. E.M.A. ex rel. Johnson*, 568 U.S. 627, 636 (2013). To determine whether such a conflict exists, courts ask whether a "private party could *independently* do under federal law what state law requires of it." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011) (emphasis added).

This conflict-preemption question arises frequently in cases where plaintiffs assert state-law failure-to-warn claims. As a general rule, the manufacturer of an FDA-approved drug "may only change a drug label after the FDA approves a supplemental application." *Wyeth v. Levine*, 555 U.S. 555, 568 (2009); *see supra* pp. 6-8. The CBE process provides "a narrow exception

to the general rule" and allows a manufacturer to make labeling claims unilaterally, subject to after-the-fact FDA approval. 73 Fed. Reg. 2848, 2850 (Jan. 16, 2008). But if that narrow exception does not apply, federal law preempts failure-to-warn claims because "a party cannot satisfy its state duties without the Federal Government's special permission and assistance." *Mensing*, 564 U.S. at 623-24.

In *Wyeth*, the Supreme Court set out a two-step inquiry governing conflict preemption in this context. Under the first step, the court determines whether "the CBE regulation allows a brand name manufacturer to make the particular type of change" allegedly required by state law. *Marcus v. Forest Lab'ys (In re Celexa & Lexapro Mktg. & Sales Pracs. Litig.)*, 779 F.3d 34, 41-42 (1st Cir. 2015). At that step, the question is whether the plaintiffs' claims rest on "newly acquired information" providing "evidence of a causal association" between the drug and a significant hazard. 21 C.F.R. §§ 314.70(c)(6)(iii)(A), 201.57(c)(6)(i). If no, preemption is required.

Even if the CBE process was available, FDA reviews CBE changes and can reject those changes if they do not satisfy the regulatory criteria. 21 C.F.R. § 314.70(c)(7); *Albrecht*, 139 S. Ct. at 1679. Accordingly, the second *Wyeth* step looks to whether "clear evidence" indicates that "FDA would not

have approved" the warning that state law requires. *Wyeth*, 555 U.S. at 571. In short, federal law preempts state-law claims if either (1) the CBE process was not available (*Wyeth* step one) or (2) "clear evidence" shows that FDA would have rejected the requested changes (*Wyeth* step two).

Plaintiffs' claims fail both *Wyeth* steps. As the district court correctly held, under the second step, clear evidence shows that FDA "would not have approved a change" to Zofran's labeling. *See id.* Alternatively, the Japanese animal studies are not "newly acquired information" that would have allowed GSK to use the CBE process. *See* 21 C.F.R. §§ 201.57(c)(6)(i), 314.70(c)(6)(iii)(A). Either way, federal law prevented GSK from unilaterally revising Zofran's labeling.

I. THE DISTRICT COURT CORRECTLY HELD THAT PREEMPTION IS REQUIRED UNDER *WYETH* STEP TWO

This is a textbook case for preemption under *Wyeth*'s second step. To satisfy that step, a defendant must provide "'clear evidence' that the FDA would not have approved the warning that state law [allegedly] requires." *Albrecht*, 139 S. Ct. at 1676. Here, that happened not once, not twice—but three times. FDA has spoken directly and conclusively on the question whether scientific evidence supports an enhanced pregnancy warning for Zofran, and, each time, FDA's position has been clear: the birth-defect warnings that

Plaintiffs propose are unwarranted and, indeed, misleading. As the district court held, permitting Plaintiffs to pursue these claims in the face of FDA's contrary judgment "might well discourage physicians from prescribing a useful pharmaceutical product that the FDA has concluded is reasonably safe." Add. 67.

A. The District Court Correctly Held that FDA's Action on Novartis's 2020 PAS Preempts Plaintiffs' Claims

FDA, with full knowledge of the Japanese animal studies, unequivocally rejected Novartis's 2020 PAS requesting an enhanced pregnancy warning. Novartis's PAS specifically addressed the Japanese studies and Dr. Danielsson's publication discussing those studies. And the PAS came shortly on the heels of FDA's meeting with Plaintiffs regarding the Japanese studies. With this evidence, FDA rejected the contention that scientific data supports a causal association between Zofran and birth defects. That rejection clearly and conclusively shows that "FDA would not have approved" Plaintiffs' desired revision to Zofran's labeling. *Wyeth*, 555 U.S. at 571.

1. FDA was fully informed of the justifications for Plaintiffs' enhanced pregnancy warning

By the time FDA reviewed Novartis's 2020 PAS, the agency unquestionably had full knowledge of the Japanese animal studies. FDA's Center for

Drug Evaluation and Research (CDER), the division responsible for approving prescription drugs and labeling, possessed the translated study reports, JA-8002-03, 8607-847, 8850-9005, 9238-98, along with translated versions of peer-reviewed Japanese publications that discussed the studies. JA-8004, 9413-83, 9486-565, 9568-606. GSK disclosed to FDA Plaintiffs' allegation that the studies "show teratogenic effect." JA-7991. And the agency possessed Dr. Danielsson's 2014 and 2018 articles setting out his hypothesis that Zofran causes birth defects, JA-7998, 9360-69, 9373-77, as well as other articles that Plaintiffs claimed supported Dr. Danielsson's causation theory, JA-7999-8000, 9609-17, 9620-26, 9629-36.

In connection with GSK's citizen petition, both GSK and Plaintiffs met with representatives of CDER to discuss the studies and their impact on Zofran's labeling. JA-9706-07, 9749-50. Plaintiffs' PowerPoint—entitled "Zofran Japanese Animal Studies and Other Material Safety Data Not Provided to FDA and Healthcare Providers in the United States"—discussed the Japanese studies in detail. JA-9764-823. For example, in a slide called "The Japanese Zofran Studies Contained Material Safety Information That a Reasonable FDA Scientist Would Have Wanted to Consider; They Were Not Repetitive of the Studies Already Provided to FDA," Plaintiffs summarized

their arguments about the Japanese studies. JA-9769. They specifically referenced Dr. Danielsson's opinions, including his opinion that "there was clear evidence of teratogenicity of ondansetron in the rat studies." JA-9771-72; *see* JA-9804-05, 9817. Plaintiffs emphasized their view that Study No. 100424 showed an "[i]ncrease in malformations with Zofran exposure compared with concurrent control animals." JA-9790. And they set out their claim that Studies No. 100423 and 100441 purportedly showed teratogenic effects. JA-9794, 9822. After that meeting, Plaintiffs submitted to FDA (1) Dr. Danielsson's expert reports; (2) the report of their regulatory expert, Dr. Harvey, (3) the transcript of Dr. Danielsson's deposition; and (4) Dr. Danielsson's 2018 publication. JA-9833-34.

Finally, as already discussed above, [redacted] SJA-1697, 1717-42, 1744-68, 1770-78; *see supra* pp. 21-22.

In short, at the time of Novartis's 2020 PAS, the agency had received all information regarding the Japanese animal studies that Plaintiffs claim to be material.

2. Clear evidence shows FDA would have rejected Plaintiffs' enhanced pregnancy warning

[redacted] SJA-1789, [redacted] SJA-1790. In doing so, FDA necessarily dismissed Plaintiffs' interpretation of the Japanese studies, and FDA reaffirmed the existing labeling's statement that the animal data "did not show evidence of harm to the fetus." JA-11030.

FDA's responses to Novartis's 2020 PAS directly refute Plaintiffs' contentions. Plaintiffs assert that a Category C warning was warranted because the "Japanese animal studies . . . show evidence of teratogenicity," Br. 12; *accord* Br. 34-36, 42-44, and provide "reasonable evidence of a causal association between Zofran and birth defects," Br. 35. But FDA concluded just the opposite. [redacted] SJA-1789, [redacted] SJA-1790. FDA could not

have written these words if the Japanese studies prove that "maternal exposure to ondansetron is associated with adverse developmental outcomes," *id.*, as Plaintiffs claim.

FDA did not stop there. As the district court recognized, FDA "approved a label that contains language that is *directly contrary* to the language proposed by plaintiffs." Add. 59 (emphasis added). Plaintiffs claim (at 2, 52) that the labeling should have warned that Zofran "has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in [rats] when given in doses (x) times the human dose." Br. 8-9 (quoting 21 C.F.R. § 201.57(c)(9)(i)(A)(3) (2007)). But FDA affirmed language stating that animal data revealed "no significant effects of ondansetron [*i.e.*, Zofran] on the maternal animals or the development of the offspring." JA-11031. FDA thus reaffirmed (for the third time) language that is diametrically opposite to the labeling that Plaintiffs argue state law required.

Courts have readily found clear evidence that FDA would not have approved a labeling change in similar circumstances. For example, in *Ridings v. Maurice*, the court found "clear evidence" that FDA would not have permitted the plaintiffs' proposed warnings when the plaintiffs' evidence "ha[d] been provided to the FDA and the FDA [did] not take[] any action to substantively alter

[the] warning on the topics at issue in th[e] litigation." 444 F. Supp. 3d 973, 998 (W.D. Mo. 2020). Similarly, in *In re Incretin-Based Therapies Products Liability Litigation*, the Court found *Wyeth*'s second step satisfied when FDA—with all the information purportedly justifying the proposed warning—approved labeling changes that did not include the proposed warning. 524 F. Supp. 3d 1007, 1032 (S.D. Cal. 2021), *aff'd*, 2022 WL 898595 (9th Cir. Mar. 28, 2022).

Courts have likewise found *Wyeth*'s second step satisfied when, as here, FDA action contradicts the premise underlying the proposed warning. In *Thomas v. Bracco Diagnostics Inc.*, for example, the court held that FDA's approval of labeling "specifically stating facts contrary to the warning sought by the Plaintiff" constituted "clear evidence that the FDA would not have approved a label change which warned of such adverse effects." 2020 WL 1016273, at *10 (W.D. La. Feb. 27, 2020), *report and recommendation adopted*, 2020 WL 1243389 (W.D. La. Mar. 13, 2020). And, on remand from the Supreme Court's decision in *Albrecht*, the district court noted that "[b]ecause the basis for the FDA's rejection was insufficient evidence of a causal link between [the drug and the purported risk], . . . the evidence is clear and convincing that the Agency would not have approved a differently worded warning no matter how

Defendant attempted to submit one." *In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, --- F. Supp. 3d ---, 2022 WL 855853, at *33 (D.N.J. Mar. 23, 2022).

In short, the district court correctly held that FDA's fully informed rejection of the safety risk raised by Plaintiffs provides clear evidence that FDA would not have approved Plaintiffs' proposed warning.

3. Plaintiffs' contrary arguments lack merit

Only on page 52 of their brief—well past the halfway mark—do Plaintiffs engage with the district court's analysis. Plaintiffs (and their amici) contend that the only way to satisfy *Wyeth*'s second step is for a drug manufacturer to request the exact warning pressed in litigation and for FDA to expressly reject that warning. Thus, Plaintiffs argue, because Novartis did not propose to warn that animal studies in particular show that Zofran causes birth defects, FDA's action on Novartis's PAS lacks preemptive effect. Each of Plaintiffs' attempts to support that contention fails.

1. Plaintiffs first argue (at 53) that FDA's rejection of Novartis's PAS does not support preemption because "there is no evidence that FDA ever *considered* the Japanese animal studies in the entire regulatory history of Zofran." Plaintiffs claim that, even though Novartis presented the Japanese

studies to FDA, Novartis "did not ask FDA to *consider* the Japanese animal data" because Novartis "told FDA that those studies contained no evidence of teratogenicity and did not ask for any changes to the relevant sections of the label." Br. 53 (emphasis added). That argument cannot withstand even minimal scrutiny.

As an initial matter, *Wyeth*'s second step does not require evidence of FDA's internal decision-making process. *Albrecht* itself compels this point. The Court explained that the "meaning and scope" of FDA action depends on "*what information the FDA had before it*." 139 S. Ct. at 1680 (emphasis added). The Court thus focused the analysis on the objective inputs into FDA's decision-making process, not a subjective inquiry into FDA deliberations. "It is not the function of the court to probe the mental processes of administrative officers." *Braniff Airways v. C.A.B.*, 379 F.2d 453, 460 (D.C. Cir. 1967) (citation omitted). Plaintiffs cite no contrary law supporting their novel "consideration" theory.

The Supreme Court's focus on the evidence *available* to FDA is unsurprising: Only FDA can speak to the information it subjectively *considered*. Plaintiffs' position would require parties to seek discovery and testimony from the agency. As FDA has previously explained, intrusive inquiries into FDA's

deliberations "would pose a significant potential for diverting FDA's resources from the important health mission that Congress has assigned to it and for distorting FDA's internal decisionmaking processes." U.S. Br. at 10-11, *Buckman Co. v. Plaintiffs' Legal Comm.* (No. 98-1768), 2000 WL 1364441 ("*Buckman* Br."); *see also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001). Indeed, FDA denied Plaintiffs' letter request to depose FDA officials in this case because depositions would "divert manpower and resources from FDA's public health mission." Dkt. No. 1847-1.

Even were the relevant legal inquiry whether the agency "considered" information, Plaintiffs' claims would still be preempted. As the district court recognized, the fact "that the FDA was not asked to *change* the animal-data label does not mean that it was not asked to *consider* that information." Add. 60. All that matters is that Novartis disclosed and submitted the Japanese animal studies and Dr. Danielsson's opinion regarding those studies for FDA's consideration. *See supra* p. 45. And even beyond that, Plaintiffs themselves asked FDA to consider the Japanese animal studies. *Supra* pp. 19-20, 39-40.

Plaintiffs cannot explain why FDA would not have considered the animal studies *directly presented to it*. The most they muster is to hint that FDA would not have considered the studies because they constitute "thirty-year-

old evidence." *E.g.*, Br. 52, 53, 63. But Plaintiffs cannot have it both ways. The Japanese studies cannot be both so important that they would prompt FDA to approve a labeling change it has rejected three times but so old that FDA would not consider them important enough to read (even after Novartis, GSK, and Plaintiffs drew FDA's attention to the studies).

On this extraordinary record, it is inconceivable that an expert public-health agency would ignore these studies and allow a potential safety issue to go unaddressed, leaving pregnant women at risk. Plaintiffs' suggestion is not only insulting to FDA's dedicated public servants, it disregards the presumption of regularity that requires courts to presume that FDA officials properly discharged their official duties, including by "conscientiously consider[ing] the issues" before them. *Braniff Airways*, 379 F.2d at 460.

Plaintiffs' argument further disregards the agency's actions in this case. In denying GSK's citizen petition, the agency emphasized that the "evaluation" of "proposed labeling changes"—like those proposed by Novartis—"requires the review of *all* relevant information before the Agency." JA-10482 (citing 21 C.F.R. § 201.57(b)(9)(i)(B)); *see supra* pp. 20-21. In other words, FDA said it would consider all relevant information, which includes the animal

studies. What is more, as the district court recognized (Add. 28), when considering Novartis's 2020 PAS, FDA *sua sponte* added language to the "Animal Data" subsection for the labeling for one formulation "to clarify the route of administration of ondansetron," proving conclusively that FDA considered the animal data. *See* JA-11019, 11031. This is yet another devastating fact that Plaintiffs bury in a footnote (at 56 n.19).[9] [redacted] SJA-1790 [redacted]

At a minimum, the district court did not clearly err in finding that FDA "considered the . . . evidence that plaintiffs contend requires an enhanced warning," including the Japanese animal studies. *See* Add. 62-63; *supra* pp. 34-35 (clearly erroneous standard applies to resolution of subsidiary factual disputes). The court oversaw this litigation for over five years. It watched the relevant interactions with FDA unfold in real time and even corresponded with FDA itself. *See supra* p. 27. Given that history and the sheer implausibility of

[9] Plaintiffs contend (at 56 n.19) that FDA's edit only conformed various versions of the labeling and suggest that FDA did not even look at the underlying studies, but FDA said that it intended the edit "to clarify the route of administration of ondansetron" in the referenced study. JA-11019.

Plaintiffs' contention that FDA turned a blind eye to relevant safety information on these facts, Plaintiffs cannot establish clear error under their legally erroneous "consideration" test.

2. Plaintiffs next argue (at 54-59) that FDA did not reject the verbatim warning Plaintiffs propose, characterizing anything short of that rejection as "FDA Silence." That argument misunderstands both the facts and the law.

As a factual matter, FDA did reject the substance of the warning that Plaintiffs now desire, *i.e.*, that animal studies show that Zofran causes birth defects. [redacted] *see supra* p. 15 [redacted] SJA-1674. That rejected warning is the same warning that the master complaint alleges GSK should have provided. *See* JA-197 (¶ 52) ("the use of ondansetron in pregnancy is not recommended").

[redacted] SJA-1676. In expressly disapproving a warning that Zofran *possibly* could be teratogenic, FDA necessarily rejected an even stronger warning that Zofran *is* teratogenic. That Novartis did not restate its

proposed warnings in the "Animal Data" subsection is irrelevant. *See Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 814 (7th Cir. 2018) (rejecting as "unreasonable" plaintiffs' argument that FDA rejected proposed warning only because the manufacturer "proposed putting it in the wrong place," and granting preemption).[10]

In any event, *Albrecht* does not require express disapproval of the verbatim warning urged by plaintiffs in litigation. As a general matter, "[c]ourts have universally rejected the notion that [*Wyeth*'s second step] requires a showing that the manufacturer attempted to apply the warning suggested by the plaintiff" and had that labeling "rejected by the FDA." *Cerveny v. Aventis, Inc.*, 155 F. Supp. 3d 1203, 1214 (D. Utah 2016), *aff'd in part, rev'd in part*, 855 F.3d 1091 (10th Cir. 2017). Plaintiffs suggest that *Albrecht* changed that rule

[10] Plaintiffs suggest in a footnote (at 58 n.20) that FDA's decision to "permit[] Novartis to include data from multiple human epidemiological studies" in the "Human Data" subsection means that FDA would have "permitted Novartis to add information about birth defects in the Japanese studies to the labeling." The PLLR, however, *requires* a narrative description of the available epidemiological and animal data. *See supra* p. 15. That FDA approved revisions to the "Human Data" narrative but did not revise the "Animal Data" narrative (with the one exception described above) simply proves that FDA did not think the Japanese studies warranted changing the "Animal Data" subsection.

by holding that a manufacturer must show that FDA "informed the drug manufacturer that the FDA would not approve changing the drug's label to include [the] warning [required by state law]." 139 S. Ct. at 1678. That argument misunderstands *Albrecht*.

Albrecht did not silently replace *Wyeth*'s would-not-have-approved standard with an "express disapproval requirement." Br. 57-59. Quite the contrary, the Court embraced *Wyeth*. *Albrecht* started its analysis by citing *Wyeth*'s "would not have approved" inquiry, 139 S. Ct. at 1676, and noted that *Wyeth*'s "conclusions flow from our precedents on impossibility preemption and the statutory and regulatory scheme that we reviewed in *Wyeth*," *id.* at 1678. The Court went on to state that "if the FDA rejected a drug manufacturer's supplemental application to change a drug label on the ground that the information supporting the application was insufficient to warrant a labeling change, *the meaning and scope of that decision* might depend on what information the FDA had before it"—an inquiry entirely incongruent with a requirement that FDA expressly reject the warning proposed by plaintiffs. *Id.* at 1680.

Since *Albrecht*, courts have repeatedly disagreed with the notion that *Albrecht* imposes an express disapproval requirement. As a general matter,

the Seventh Circuit in *Dolin* rejected the contention that *Albrecht* "adopt[ed] a new rule of preemption law." *Dolin v. GlaxoSmithKline LLC*, 951 F.3d 882, 891 (7th Cir. 2020). Numerous other courts have likewise held that *Albrecht* did not effectuate a sea change in preemption. *See Cerveny v. Aventis, Inc.*, 783 F. App'x. 804 n.9 (10th Cir. 2019) (dismissing contention that "only labeling changes sought by the manufacturer can lead to preemption" notwithstanding *Albrecht*); *In re Fosamax*, 2022 WL 855853, at *12 ("[N]ot one court has interpreted [*Albrecht*] to establish a new standard for impossibility preemption requiring actual agency or manufacturer action."); *In re Incretin-Based Therapies*, 524 F. Supp. 3d at 1017 (stating that the court does not read *Albrecht* to "limit[] preemption to cases where the manufacturer has proposed a label change"); *Silverstein v. Boehringer Ingelheim Pharm., Inc.*, 2020 WL 6110909, at *9 (S.D. Fla. Oct. 7, 2020) ("[Preemption] can be satisfied even if the labeling change has not been presented to, and rejected by, the FDA."); *Ridings*, 444 F. Supp. 3d. at 991, 998 (noting *Albrecht*'s "cryptic . . . guidance" and finding a proposed warning preempted where FDA did not revise labeling after receiving information justifying that warning). Plaintiffs offer no contrary law.

Notably, on remand in *Albrecht*, the district court rejected an argument identical to Plaintiffs'. *See In re Fosamax*, 2022 WL 855853, at *12. There, plaintiffs argued that "*Merck* repudiates *Wyeth*'s premise that a manufacturer can show preemption by arguing that the FDA *would have* rejected a warning that it did not actually reject." *Id.* (internal quotation marks omitted). The district court rejected that premise. *Id.* Because, as here, FDA rejected the manufacturer's proposed warning on the ground that "FDA doubted the evidence linking [Fosamax] to atypical femoral fractures in a causal sense," the court concluded that FDA would have rejected a differently worded warning as well. *Id.* at *26-32. It thus found the plaintiffs' claims preempted.

Plaintiffs suggest (at 55-56) that the Court cannot draw any meaning from FDA's actions because FDA did not expressly discuss the animal studies. That argument, however, assumes that FDA did not consider the Japanese animal studies. As already discussed, that assumption is incorrect; indeed, the agency revised the "Animal Data" section of the labeling. *See supra* pp. 25, 48. Plaintiffs' argument also blatantly disregards the agency's statutory obligation to require a labeling change if it "becomes aware of new information, including any new safety information" that it "determines should be included

in the labeling of the drug." 21 U.S.C. § 355(*o*)(4)(A). As the government explained in *Albrecht*, if the agency thought that Plaintiffs' information should have been included in the labeling, section 355(*o*)(4)(A) would have obligated FDA to act to protect public health and safety. *Albrecht* Br. at 21-22. Courts thus have rejected plaintiffs' attempts to evade preemption on strained theories that gin up a "factual dispute . . . based on speculation that the FDA would jettison its legal requirements" or "scuttle[] its own regulatory standard." *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1103 (10th Cir. 2017). Such "conjectures" do not "suffice to prevent federal and state law from conflicting for Supremacy Clause purposes." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 621 (2011).

To be sure, a manufacturer "bears responsibility for the content of its label at all times," Br. 62 (quoting *Wyeth*, 555 U.S. at 570-71); it must inform FDA of newly emerging or newly discovered risks. But once FDA becomes fully aware of the pertinent information—which, here, Novartis, GSK, and Plaintiffs provided to FDA—the "meaning and scope" of the agency's actions must account for its statutory obligations. *See Albrecht*, 139 S. Ct. at 1680; *see also id.* at 1684 (Alito, J., concurring in the judgment); *In re Incretin-Based Therapies*, 524 F. Supp. 3d at 1033 ("[T]he Court cannot simply ignore the

FDA's demonstrated commitment to actively and continuously monitoring the [drug].").

Plaintiffs' novel position conflicts with the regulatory scheme and threatens to overwhelm FDA's resources. Manufacturers *cannot* propose amendments that they believe are unwarranted: "[i]t is technically a violation of federal law to propose a CBE that is not based on reasonable evidence." *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010); *see also Albrecht*, 139 S. Ct. 1679. The policy implication of an express disapproval directive, moreover, is clear: No matter how many times FDA declines a request to change labeling or how clearly the agency rejects a scientific theory, manufacturers seeking to avoid state-law suits would have to keep proposing amendments that FDA would not allow. *Wyeth* does not require such a nonsensical rule. *Cf. Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1279 (W.D. Okla. 2011) ("[T]his court does not interpret [*Wyeth*] as imposing upon the drug manufacturer a duty to continually 'press' an enhanced warning which has been rejected by the FDA."); *In re Fosamax*, 2022 WL 855853, at *32.

3. Finally, Plaintiffs (at 60) argue that "[t]he district court's ruling . . . violates the *Albrecht* requirement that only formal agency action pursuant to its statutorily delegated authority can lead to preemption." That

argument is particularly bizarre, because Plaintiffs concede (at 61) that FDA's resolution of Novartis's 2020 PAS constituted "formal agency action" pursuant to FDA's delegated authority. That action approved language stating that animal data "did not show evidence of harm to the fetus," JA-11030—a conclusion at odds with Plaintiffs' desired labeling.

In any event, *Albrecht* does not require "formal agency action." The Court in *Albrecht* stated only that, when analyzing preemption, courts look to "agency actions taken pursuant to the FDA's congressionally delegated authority." 139 S. Ct. at 1679. While Justice Thomas's concurring opinion expressed the view that preemption requires "final agency action," *id.* at 1683, the Court declined to impose that requirement, making "only the obvious point that, whatever the means the FDA uses to exercise its authority, those means must lie within the scope of authority Congress has lawfully delegated," *id.* at 1679 (maj. op.).

Each of FDA's actions here undoubtedly falls within "the scope of authority Congress has lawfully delegated." *Id.* Congress authorized FDA to regulate the labeling of drug products, 21 U.S.C. § 355, and to enact regulations to enforce the Food, Drug, and Cosmetic Act, § 371(a). Pursuant to that authority, FDA enacted regulations governing prior approval supplements by

manufacturers like Novartis. 21 C.F.R. § 314.70(b). As Plaintiffs previously admitted in their presentation to FDA, "where a manufacturer does file such a supplemental application with the FDA, it invokes the agency's express statutory authority to determine whether the drug is safe and effective under the conditions specified in its proposed labeling in light of the best scientific information currently available." JA-9758. FDA's action on Novartis's PAS falls squarely under Congress's delegation of authority to FDA.

* * *

Because FDA rejected an enhanced pregnancy warning after obtaining the scientific data that Plaintiffs claim establishes causation, GSK cannot be liable under state law for failing to include enhanced warnings. This Court should affirm the judgment.

B. FDA's Action on the 2015 Citizen Petition and Novartis's 2016 PAS Also Preempts Plaintiffs' Claims at *Wyeth* Step Two

FDA's prior actions—first, when it denied James Reichmann's citizen petition in 2015 and, again, when it rejected in 2016 Novartis's proposed warnings—provide independent, additional "clear evidence that the FDA would not have approved" the labeling change Plaintiffs desire. *Wyeth*, 555 U.S. at 571.

Plaintiffs do not dispute that FDA rejected the very warnings that Plaintiffs claim were required in 2015 and 2016. *See* Br. 49-52. Nor could they:

FDA expressly rejected a Category C warning when it denied the Reichmann petition. *See supra* p. 14. Instead, Plaintiffs argue only that FDA's prior actions were not "fully informed" because FDA lacked the data underlying three of the Japanese animal studies when it took those actions. That argument lacks merit.

1. As the Supreme Court made clear in *Albrecht*, preemption at *Wyeth* step two does not require that the agency be "fully informed" of every single safety-related document at the time it rejects proposed warnings. Rather, the preemption inquiry asks whether "the drug manufacturer submitted all *material* information to the FDA." *Albrecht*, 139 S. Ct. at 1680 (emphasis added). Plaintiffs seemingly concede this point in their brief. *See* Br. 52 (arguing that GSK did not "fully inform . . . FDA of information *material* to the teratogenicity risk" (emphasis added)).

Any other approach would improperly usurp FDA's prerogative to define manufacturers' disclosure requirements. FDA does not require manufacturers to disclose all data from animal studies conducted anywhere at any time. FDA regulations require a manufacturer of an FDA-approved drug

to disclose in an annual report "[a] *list* of the preclinical studies (including animal studies) completed or in progress during the past year and a *summary* of the major preclinical *findings*." 21 C.F.R. § 312.33(b)(6) (emphases added).

GSK complied with this disclosure requirement in 1993, in its first annual report for Zofran. GSK disclosed, by name and study number, each Japanese study. *See* JA-3873. GSK identified the studies as "performed specifically to satisfy Japanese regulatory requirements." JA-3872. And GSK accurately summarized the "findings" of the study investigators: the studies were "repetitive" of other studies submitted to FDA that found no evidence of teratogenicity and thus "provide[d] no new significant safety information." JA-3872; *see supra* pp. 10-11 (describing findings of study investigators). Plaintiffs' regulatory expert Dr. Harvey conceded that GSK's annual report complied with FDA's disclosure requirement. JA-530.

FDA thus was fully and accurately informed of the information FDA deemed sufficiently material to warrant disclosure: a list of the Japanese studies and a summary of their "findings." 21 C.F.R. § 312.33(b)(6). Plaintiffs' contrary position would have required GSK to disclose all the data underlying the investigators' findings, in contravention of FDA regulations. Plaintiffs cannot Monday-morning quarterback FDA's disclosure regulations. As the

government has recognized, "[i]f federal regulatory agencies are to perform the important functions assigned to them by Congress, they must have the ability to decide, free from hindrances imposed by state law, how best to obtain the information they need and how to sanction those who fail to provide such information." *Buckman* Br. at 18. Plaintiffs' rule would transfer that power from the agency to the courts, incentivizing manufacturers "to submit a deluge of information that the [FDA] neither wants nor needs" and creating "additional burdens on the FDA[]." *Buckman*, 531 U.S. at 351.

Plaintiffs cite no cases holding that the "fully informed" requirement mandates that a defendant defy FDA disclosure requirements. Plaintiffs repeatedly suggest that the court below held that FDA was not fully informed of the Japanese studies until GSK's 2019 citizen petition. *See* Br. 26, 29, 49-50. Not true. The court initially held only that a fact issue existed as to whether FDA was fully informed at the time of the pre-2019 rejections, JA-394-97—a holding inconsistent with Plaintiffs' proposed *per se* rule that FDA is never informed absent the submission of full data. And, after *Albrecht*, the court did not return to this issue, given its holding that FDA's rejection of Novartis's 2020 PAS required preemption.

None of Plaintiffs' cases support its novel rule. In *In re Taxotere (Docetaxel) Products Liability Litigation*, 508 F. Supp. 3d 71 (E.D. La. 2020) (which Plaintiffs cite at 50), the manufacturer failed to "alert the FDA of any uptick in reports of permanent alopecia." *Id.* at 83. As evidence that FDA was not fully informed, the court highlighted the agency's request for an analysis of this issue years later, which ultimately prompted the addition of an alopecia warning. *Id.*

No such evidence exists here. Plaintiffs (at 17, 36) invoke FDA's 2014 request to GSK (made in a bubble comment in draft labeling) for "full details of animal reproduction studies" as it considered potential labeling revisions that were never implemented. JA-3094, 3105. But FDA's comment referred to *the U.K. animal studies* that were summarized in the existing labeling. *See* JA-3105. In response, GSK identified and summarized the U.K. studies and noted that the referenced studies were contained in GSK's original NDA. JA-3139. FDA's stray request cannot reasonably mean that any animal data—no matter how inconsequential and repetitive—are material.

Plaintiffs' other citations are even further afield. In *In re Avandia Marketing, Sales & Products Liability Litigation*, 945 F.3d 749 (3d Cir. 2019) (cited at 51), the court stated that the manufacturer did not have the pertinent

data and information until *after* FDA's rejection—which led the court to hold that FDA was not "fully informed" at the time of that rejection. *Id.* at 759. And in *In re Testosterone Replacement Therapy Products Liability Litigation*, 430 F. Supp. 3d 516, 531 (N.D. Ill. 2019), and *Risperdal & Invega Cases*, 263 Cal. Rptr. 3d 412, 425-26 (2020) (cited at 51), the pertinent information was never disclosed in *any format*. Plaintiffs ask this Court to be the first to adopt a novel "fully informed" requirement that disregards FDA disclosure requirements.

2. Regardless of FDA's disclosure requirements, the Japanese studies were not material. The best evidence of their immateriality is what happened when FDA received them.

First, when FDA received Japanese Study No. 100422 in 1997—a study that Plaintiffs' expert Dr. Danielsson claims shows evidence of teratogenicity, *see* JA-641—FDA found that the "results [of No. 100422] are comparable to those for [the U.K. counterpart study] included in the original submission." JA-2548, 2552. In other words, FDA expressly affirmed what GSK had disclosed in its annual report: the study provided no new safety information (that is, was immaterial).

Second, when FDA received the remaining Japanese studies in 2019 and 2020 and heard a detailed presentation from Plaintiffs' counsel about the studies, FDA again rejected enhanced pregnancy warnings. For the reasons already discussed, if the Japanese studies provided *materially* new information about Zofran's safety profile, FDA could not and would not have reapproved the existing "Animal Data" portion of the labeling. *See supra* pp. 41-43, 53-54. That FDA rejected materially identical warnings in 2015, 2016, and 2021 proves beyond any doubt that FDA was fully informed of all material information in 2015 and 2016.

II. ALTERNATIVELY, PREEMPTION IS REQUIRED UNDER *WYETH* STEP ONE

Plaintiffs' claims are independently preempted under the first step of *Wyeth* because the CBE regulation would not have "allowed [GSK] to use the CBE procedure to alter the FDA label in the manner that plaintiffs allege is necessary." *In re Celexa*, 779 F.3d at 43. A drug's manufacturer can unilaterally strengthen a drug's labeling under the CBE process only if (1) "newly acquired information" (2) shows "evidence of a causal association" between the drug and a clinically significant hazard. 21 C.F.R. § 314.70(c)(6)(iii)(A); *Albrecht*, 139 S. Ct. at 1673. Plaintiffs failed to establish the existence of any such evidence—"a necessary step in defeating [GSK]'s preemption defense." *In re*

Celexa, 779 F.3d at 41; *see also Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019). This Court may affirm on this alternative ground. *Houlton Citizens' Coal. v. Town of Houlton*, 175 F.3d 178, 184 (1st Cir. 1999).

1. Plaintiffs failed to identify "newly acquired information" that would have permitted GSK to invoke the CBE process. FDA regulations define "newly acquired information" as "data, analyses, or other information not previously submitted to the [FDA]" that "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 314.3(b).

The three Japanese studies identified by Plaintiffs do not "reveal risks of a different type or greater severity or frequency than" information already available to FDA—namely the data in the U.K. studies and Japanese Study No. 100422. *See id.* As the following chart demonstrates, the U.K. and Japanese studies paralleled each other. The studies highlighted in yellow are the ones that Plaintiffs claim are "newly acquired information."

Species	Route	U.K. Studies		Japanese Studies	
		Preliminary	Definitive	Preliminary	Definitive
Rats	Oral	R10564	R10590	100421	100422
Rats	IV	R10874*	R10937	100423	100424
Rabbits	Oral	L10565	L10649	881001* 881002	100441
Rabbits	IV	L10867*	L10873		

* Non-pregnant animals were used.

The data from the U.K. studies and Japanese Study No. 100422 showed some occurrences of adverse fetal outcomes, including increased embryofetal death and one ventricular septal defect (VSD) in Study No. 100422. *See* JA-2335-40, 2548. Using their scientific judgment, however, FDA and study investigators concluded that these occurrences were not related to Zofran. JA-2335-36 (R10937); JA-2336-37 (L10873); JA-2337-38 (R10590); JA-2338-40 (L10649); JA-2552 (100422); JA-5664, 5670 (R10590); JA-5875, 5885 (L10649); JA-6377, 6382 (L10873); JA-6546-49 (R10937). The three Japanese studies Plaintiffs point to as smoking guns revealed risks of the same type, severity, and frequency as the U.K. studies and Japanese Study No. 100422:

Japanese Study No. 100423. Plaintiffs allege (at 34) that Japanese Study No. 100423 (a preliminary study intended to select appropriate dosing for Study No. 100424) found an increase in embryofetal death. The independent study investigators, however, reported no increase in embryofetal deaths and, in fact, found no significant differences between the treatment and control groups with respect to any outcomes. JA-4294, 4314-51. Plaintiffs' expert, Dr. Harvey, admitted that this study found no fetal malformations and was

"clean." JA-532-38. Dr. Danielsson's opinion on the study is unclear. Regardless, U.K. Study L10873 reported an increase in embryofetal deaths, so this risk (assuming it exists) was known to FDA. JA-2336-37.

Japanese Study No. 100424. Plaintiffs claim (at 34) that Japanese Study No. 100424 shows an increase in embryofetal death and malformations, including two VSDs. The study investigators, however, found that Zofran "was considered to have no teratogenicity" based on the results. JA-4390. The investigators cited to background control data, which demonstrates that VSDs occur spontaneously in up to 3.01% of the relevant strain of rats. *See* JA-4390 n.7, 4392; *see also* JA-2855-56. Given that background rate, one would expect to see up to five VSDs in the high-dose group of 173 fetuses. The two VSDs observed in that group thus were well within the background rate. *See id.* This study reveals no new risk: FDA had reviewed U.K. Study L10873, which showed an increase in fetal deaths, and Japanese Study 100422, which reported one VSD and visceral malformations. JA-2336-37, 2541, 2548.

Japanese Study No. 100441. Plaintiffs allege (at 35) that Japanese Study No. 100441 shows an increase in skeletal defects through decreased ossification. The basis for this allegation is unclear. The study investigators did

not find any fetal lethal or teratogenic effect; they concluded that the decreased ossification resulted from decreased food consumption and maternal weight loss and not from exposure to Zofran. JA-4767, 4782-84. Dr. Danielsson agreed with the study investigators that these outcomes were "not directly related to ondansetron exposure." JA-650. Dr. Harvey likewise admitted that no fetal malformations were observed in the study. JA-532-33. Regardless, GSK submitted to FDA three U.K. studies reporting skeletal defects and decreased ossification (L10873, R10590, and L10649). JA-2336-40.

The Japanese animal studies thus did not "present[] a different type of risk than those the company had discussed with the FDA, or more severe or more frequent than . . . events that the government already knew about." *Gibbons*, 919 F.3d at 708. Unlike in *In re Taxotere*, 508 F. Supp. 3d at 84-85, FDA *knew* about the fetal defects, adverse outcomes, and embryofetal deaths reported in the U.K. studies and Japanese Study No. 100422, and "nonetheless did not require the defendants specifically to warn of it in the label." *Knight v. Boehringer Ingelheim Pharms.*, 984 F.3d 329, 338 (4th Cir. 2021) (finding no "newly acquired information" in a similar situation). The government, interpreting its own regulations, has stated: if "FDA previously determined that

that evidence of X was insufficient to warrant a warning about risk Y, the existence of additional but similar information about X would be insufficient to justify a warning." *Albrecht* Br. at 28 n.11. That is exactly the case here.

Critically, Plaintiffs never argued below that the three Japanese studies revealed risks different or more severe or frequent than the risks disclosed by the U.K. studies and Japanese Study No. 100422. *See generally* SJA-1477-530. Although Plaintiffs now assert (at 11) that the U.K. studies "did not generally show evidence of teratogenicity" while the Japanese studies *do* show such evidence, that claim is a change in position and contradicts their expert's opinion. Below, Dr. Danielsson opined that two of the U.K. studies contained "substantial" evidence that Zofran causes birth defects, JA-712; he just disagreed with FDA's contrary conclusion drawn from the U.K. studies. So too, Dr. Danielsson opined below that Japanese Study No. 100422, which FDA *did* review in 1997, provides evidence that Zofran causes birth defects. *Id.* Again, he disagreed with FDA's contrary conclusion.

Lest there be any doubt about this, Plaintiffs told FDA in their March 30, 2020 meeting that Dr. Danielsson's opinion was that two U.K. studies, Japanese Study No. 100422, and Japanese Study No. 100424 all showed causation of birth defects:

> [W]here the dose levels modestly exceeded human therapeutic exposure, some dose levels, the three IV studies, two in rats [a U.K. rat study and Japanese Study No. 100424], and one in rabbits [a U.K. study], and the Japanese oral study [Japanese Study No. 100422], there was a substantial increase in malformations in ondansetron dosed groups compared to untreated controls (vehicle).

JA-9772; *see also* JA-10207. That opinion thus reflects Dr. Danielsson's view that FDA was wrong to conclude that the U.K. studies and Japanese Study No. 100422 do not provide evidence that Zofran causes birth defects. Dr. Danielsson did not opine that the three Japanese studies that Plaintiffs now invoke present different risks than the studies already available to FDA.

Plaintiffs' dosing and exposure discussion (at 12, 34-36, 40-41) also departs from FDA's considered view—and even from their own expert's opinion. Plaintiffs claim (at 36) that "the U.K. studies failed to dose subject animals at a level equivalent to that which a pregnant woman and her developing embryo would be exposed, making it less likely that those studies would reveal evidence of teratogenicity." The current FDA-approved labeling for the oral formulation, however, states that "[a]t dose of 15 mg/kg/day in rates and 30 mg/kg/day in rabbits, the maternal exposure margin [during the animal studies] was *approximately 6 and 24 times the maximum recommended human oral dose* of 24 mg/kg, respectively, based on body surface area." JA-11055

(emphasis added), *see also* JA-11031 (injectable formulation). And while Plaintiffs purport to rely on Dr. Danielsson's expert report for their dosing arguments, Dr. Danielsson himself admitted that two U.K. studies and Japanese Study No. 100422 included dose levels that exceeded human exposure. *See* JA-10207, 9772 ("the dose levels modestly *exceeded human therapeutic exposure* . . . [in] the three IV studies, two in rats [R10937 and 100424] and one in rabbits [L10873] and the Japanese oral study [100422]").

Put simply, FDA agreed with the study authors, GSK, Novartis, and GSK's experts[11] that the Japanese animal studies show no new evidence of teratogenicity. *See* JA-7301. Plaintiffs cannot overcome preemption by offering an opinion that FDA got the science wrong. *See In re Celexa*, 779 F.3d at 42-43.

Plaintiffs also invoke (at 45) the opinion of their regulatory expert Dr. Harvey that the Japanese studies reflect a new degree of risk and constitute "newly acquired information." But that is a legal question for this Court to resolve. Dr. Harvey's opinion cannot help the Court answer that question. Dr. Harvey did not purport to interpret the studies or offer a scientific opinion

[11] *See* JA-7400-7636.

about what the studies mean. JA-7326. Incredibly, he *did not even read the studies* that form the basis of his "opinions." JA-7328-30. Dr. Harvey claimed that the "content" of the animal studies was "not . . . material to [his] regulatory opinion that it should have been submitted to FDA for their review." JA-7330. But the studies' contents are surely important to whether they reveal new risks and thus qualify as "newly acquired information."

In short, Plaintiffs fail to "conclusively establish, by scientifically valid measurable and statistically significant data, that the different or increased risks are actual and real." *Lyons v. Boehringer Ingelheim Pharms., Inc.*, 491 F. Supp. 3d 1350, 1364 (N.D. Ga. 2020).

2. Even if the Japanese studies revealed differing risks, they did not provide "reasonable evidence of a causal association" between Zofran and clinically significant hazards, as required by the CBE regulation. 21 C.F.R. §§ 201.57(c)(6)(i), 314.70(c)(6)(iii). FDA has already resolved this issue. With full knowledge of the studies and Plaintiffs' experts' opinions, [redacted] *See* SJA-1790 [redacted] As discussed above, even Plaintiffs' epidemiological

expert agrees with FDA that the evidence does not prove an association between Zofran and heart defects. *See supra* p. 30.

That FDA continues to reject any suggestion of a causal association between Zofran and birth defects resolves the question whether reasonable evidence of a causal association exists. *See, e.g., In re Incretin-Based Therapies*, 524 F. Supp. 3d at 1029 (finding no "evidence of a causal association" when FDA "published its findings regarding the pancreatic safety of incretin mimetics, commented on the adequacy of the drug labeling, and maintained its position that scientific evidence of a causal association between incretin-based therapies and pancreatic cancer is indeterminate"); *Drescher v. Bracco Diagnostics*, 2020 WL 1466296, at *5 (D. Ariz. Mar. 26, 2020) (finding no "reasonable evidence of a causal association" where plaintiffs' theory of "causal association between the drug and the adverse event" was "contradicted by FDA warnings"); *see also Knight*, 984 F.3d at 339 (concluding that no "newly acquired information" exists where "FDA has continued to approve labels with no monitoring requirement").

Plaintiffs (at 44) point to Dr. Harvey's claim that FDA would have considered the existence of "3 VSDs across 4 of the Japanese animal studies" *(i.e.*, Nos. 100422 and 100424) to be "evidence of a possible association." JA-802.

"Possible association," however, is not the standard for adding a warning under the CBE regulation; the newly acquired information must contain "reasonable evidence of a causal association." 21 C.F.R. § 201.57(c)(6)(i). Even were Dr. Harvey applying the right standard, his opinion would contradict FDA's express statements and final actions.

In any event, FDA does not draw conclusions from animal studies by looking at raw numbers of defects. Rather, FDA has defined a "positive signal" as "a biologically meaningful difference in dosed animals compared to concurrent or historical controls." JA-1555-56; *see also*, *e.g.*, JA-1657. The agency has repeatedly found that signal lacking. *See supra* pp. 14-18, 21-25, 41-44, 49. This Court should reject Plaintiffs' invitation to rely on "conjecture and hypothesis" to second-guess FDA's scientific judgment on that question. *Lyons*, 491 F. Supp. 3d at 1364 (quoting *Pradaxa Cases*, 2019 WL 6043513, at *3 (Cal. Super. Ct. Nov. 8, 2019)).

Without "newly acquired information" that showed "evidence of a causal association" between Zofran and birth defects, GSK could not have used the CBE regulation to amend the drug labeling—and, by extension, Plaintiffs' claims cannot survive preemption under the first step of *Wyeth*. 21 C.F.R. § 314.70(c)(6)(iii)(A).

* * *

FDA has rejected enhanced pregnancy warnings three times. The warnings that Plaintiffs advocate would mislead doctors and patients and discourage use of a drug that serves an important medical need. Because it was impossible for GSK to add Plaintiffs' unscientific warnings to Zofran's labeling, the district court correctly held that federal law preempts Plaintiffs' claims.

CONCLUSION

The Court should affirm the judgment of the district court.

May 16, 2022

Respectfully submitted,

/s/ *Lisa S. Blatt*

SCOTT A. CHESIN
SHOOK, HARDY & BACON
2555 Grand Blvd
Kansas City, MO 64108
(816) 474-6660

LISA S. BLATT
AMY MASON SAHARIA
J. MATTHEW RICE
JAMI M. KING
WILLIAMS & CONNOLLY LLP
680 Maine Avenue, SW
Washington, DC 20024
(202) 434-5000

CERTIFICATE OF COMPLIANCE

This brief complies with the typeface and type style requirements of Fed. R. App. P. 32(a)(5)(A) and Fed. R. App. P. 32(a)(6) because it has been prepared in a proportionally spaced typeface using Word 2019, in 14-point CenturyExpd BT.

This brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B) as extended by this Court in its May 13, 2022 order because it contains 14,916 words excluding the parts exempted by Fed. R. App. P. 32(f).

DATED: May 16, 2022

Respectfully submitted

/s/ *Lisa S. Blatt*
Lisa S. Blatt

CERTIFICATE OF SERVICE

I hereby certify that on May 16, 2022, I electronically filed the foregoing document with the United States Court of Appeals for the First Circuit by using the appellate NextGen system. I certify that all participants in the case are registered NextGen users and that service will be accomplished by the appellate NextGen system.

DATED: May 16, 2022

Respectfully submitted

/s/ *Lisa S. Blatt*
Lisa S. Blatt