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

BRIEF FOR PLAINTIFFS-APPELLANTS

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March 16, 2022

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REASONS WHY ORAL ARGUMENT SHOULD BE HEARD

Plaintiffs-Appellants respectfully request oral argument. This appeal represents this Court's first opportunity to address "clear evidence" impossibility preemption since the Supreme Court decided *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (U.S. 2019), and thus raises issues that have not been authoritatively decided in this Circuit. Moreover, the drug at issue, Zofran, has a lengthy and complicated regulatory history. Oral argument would assist the Court in analyzing the issues presented.

INTRODUCTION

This appeal arises out of a multi-district litigation ("MDL") proceeding concerning the prescription drug Zofran (generic name: ondansetron). Plaintiffs-Appellants ("Plaintiffs") contend that the use of Zofran during pregnancy caused their babies to be born with birth defects—either orofacial defects or cardiac defects. Plaintiffs allege, *inter alia*, that Appellee GlaxoSmithKline LLC ("GSK") failed to warn Plaintiffs' healthcare providers of the risk of birth defects associated with use of Zofran during the first trimester.

Zofran is an anti-emetic, *i.e.*, a drug to treat nausea and vomiting. FDA has only approved Zofran for chemotherapy, radiation, and post-operative nausea and vomiting. FDA has never approved Zofran for the treatment of nausea and vomiting during pregnancy, also known as morning sickness.

Zofran has, nevertheless, been widely prescribed "off-label" to pregnant women (that is, for a use not approved by FDA). While a physician can legally prescribe a drug off-label, a pharmaceutical company may not market its drug for an unapproved use. GSK improperly and aggressively promoted the use of Zofran to Obstetrician-Gynecologists ("OB/GYNs") for morning sickness. GSK took advantage of FDA's classification of Zofran as a "Pregnancy Category B" drug, a designation which, in short, meant that pre-clinical animal reproductive studies had revealed no evidence that the drug caused harm to the fetus. Unbeknownst to FDA,

however, GSK was in possession of animal studies from Japan that *did* show evidence of fetal harm, which the company withheld from the agency from 1991 until 2019. This withheld evidence would have required Zofran to be classified in "Pregnancy Category C," the category for drugs where animal studies *have* revealed adverse effects on the fetus, including birth defects.

The district court dismissed Plaintiffs' claims, granting GSK's motion for summary judgment on grounds of impossibility preemption. The court based this ruling on FDA's failure to add a warning against use during pregnancy in 2021, after the agency had finally been provided with the Japanese animal studies. This was reversible error. *See Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (U.S. 2019). FDA took no formal agency action to reject labeling that reflected the risk revealed in the Japanese animal studies; nor did it expressly inform the drug manufacturer that such a warning would not be permitted. Thus, GSK has not satisfied the "demanding" requirements of the impossibility preemption defense articulated by the United States Supreme Court in *Wyeth v. Levine*, 555 U.S. 555, 573 (2009), and in *Albrecht*.

JURISDICTIONAL STATEMENT

The United States District Court for the District of Massachusetts had diversity jurisdiction pursuant to 28 U.S.C. § 1332(a)(1) over each case in this MDL, as the amounts in controversy exceed $75,000.00, and GSK and Plaintiffs are citizens of different states. PUB_000187.[1] This MDL was transferred to the district for coordinated pretrial proceedings pursuant to 28 U.S.C. § 1407 by the Judicial Panel on Multidistrict Litigation ("JPML"). *In re Zofran (Ondansetron) Prods. Liab. Litig.*, 138 F. Supp. 3d 1381 (J.P.M.L. 2015).

The district court entered final judgment dismissing Plaintiffs' claims on June 2, 2021.[2] PUB_011066. Plaintiffs filed a timely notice of appeal on July 1, 2021. PUB_011078. This Court has appellate jurisdiction pursuant to 28 U.S.C.

[1] The Joint Appendix has been divided into volumes of public documents, cited as PUB_000001 et seq., and a sealed volume of unredacted copies of documents designated as confidential, cited as UR_00001 et seq.

[2] The district court inadvertently excluded five cases from the list of cases subject to its entry of final judgment on June 2, 2021. PUB_011066. The Plaintiffs' Steering Committee ("PSC") notified the clerk's office of this error prior to filing its Notice of Appeal. PUB_011078. The PSC filed its Notice of Appeal on behalf of all Plaintiffs—including those inadvertently excluded—on July 1, 2021. *Id.* The district court then amended its entry of final judgment on July 8, 2021 to include those five cases. PUB_011081. Rule 4(a)(2) treats the Notice of Appeal in those cases as having been filed on the date final judgment was entered. *See* Fed. R. App. P. 4(a)(2) ("A notice of appeal filed after the court announces a decision or order—but before the entry of the judgment or order—is treated as filed on the date of and after the entry."). Thus, for those five cases, the Notice of Appeal is treated as timely filed on July 8, 2021.

§ 1291 and Federal Rule of Appellate Procedure 4(a), as this appeal is from a final judgment disposing of all claims.

STATEMENT OF THE ISSUES PRESENTED FOR REVIEW

Did the district court err in holding Plaintiffs' claims to be preempted by federal law?

STATEMENT OF THE CASE

I. FACTUAL BACKGROUND

A. Zofran

Zofran is a prescription drug approved for the prevention of (1) chemotherapy-induced nausea and vomiting; (2) radiation therapy-induced nausea and vomiting; and (3) post-operative nausea and vomiting. PUB_001391. Zofran has never been FDA-approved for pregnancy-related nausea and vomiting.

Zofran is part of a class of anti-emetics referred to as selective serotonin 5-HT3 receptor antagonists. PUB_001391. Serotonin is a neurotransmitter found in most tissues of the human body. PUB_000188. Zofran is believed to inhibit the body's serotonin signaling, thereby alleviating symptoms of nausea and vomiting. *Id*. Zofran has caused serious injuries in patients using the drug, including sometimes fatal cardiac arrhythmias, such as QT prolongation and Torsade de Pointes, and serotonin syndrome. PUB_001391.

Serotonin signaling also regulates developmental processes that are critical to normal embryonic development. PUB_000188. Inhibiting serotonin signaling during embryonic development increases the risk of birth defects. PUB_000188.

GSK owned Zofran from 1991, when it received FDA approval, through March 2015. PUB_000261. At that time, GSK sold the rights to manufacture and market the drug to Novartis Pharmaceuticals Corporation ("Novartis"). *Id.*

B. Federal Law on Drug Labeling

A drug company may not market or sell a new pharmaceutical drug without the approval of FDA. *See* 21 U.S.C. § 355(a). To obtain that approval, the company must submit a New Drug Application ("NDA"), which must include comprehensive information about the drug, including its formulation, its proposed labeling, and scientific data about its safety and efficacy. *Id.* § 355(b)(1)(A)(i), (iii), (vi); 21 C.F.R. §§ 314.50(d)(5)(viii), 201.57(a). FDA regulations require that an NDA fully disclose all "pertinent" safety information. *See, e.g.*, 21 C.F.R. §§ 314.50 (requiring "reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source"); 314.50(d)(5)(vi)(a) (requiring "an integrated summary of all available information about the safety of the drug product, including pertinent animal data [and] demonstrated or potential adverse effects of the drug").

1. Pregnancy Labeling

FDA regulations govern the use of drugs during pregnancy. To gain FDA approval, sponsors must conduct animal toxicology studies, including reproductive toxicology studies to investigate any potential effects on the fetus. *See* 21 C.F.R. § 312.23(a)(8)(ii)(a) (sponsor must include an "integrated summary of the

toxicological effects of the drug in animals," including "tests of the drug's effects on reproduction and the developing fetus").

Until 2015, FDA regulations classified drugs into five categories of safety for use by pregnant women: A, B, C, D, or X. Categories B and C are most relevant to this appeal. According to the then-applicable regulation, "[i]f animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women," the label must state:

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

21 C.F.R. § 201.57(c)(9)(i)(A)(2) (2007).

By contrast, "[i]f animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks," FDA regulations required the label to carry the following warning language:

> **Pregnancy Category C**. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women.

> (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

21 C.F.R. § 201.57(c)(9)(i)(A)(3) (2007).[3]

On June 30, 2015, FDA changed the pregnancy labeling rules for prescription drugs. The new regulation eliminated the pregnancy categories. The agency explained that:

> FDA learned that the pregnancy categories were heavily relied upon by clinicians but were often misinterpreted and misused in that prescribing decisions were being made based on the pregnancy category, rather than an understanding of the underlying information that informed the assignment of the pregnancy category.

PUB_012087. Instead, FDA now requires a "summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation." *Id.* This is known as the "Pregnancy and Lactation Labeling Rule" or "PLLR." *Id.*

2. Procedures for Changing a Drug's Labeling

Knowledge about the safety and efficacy of a drug may change over time. For that reason, a "central premise of federal drug regulation [is] that the manufacturer bears responsibility for the content of its label at all times." *Levine*, 555 U.S. at 570–

[3] "Teratogenic" is the term for a drug that may cause adverse effects, including birth defects, to a fetus; "embryocidal" refers to the death of the fetus.

71. "It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* at 571.

A drug company may change a drug's labeling in two ways. *See In re Celexa & Lexapro Mktg. & Sales Pracs. Litig.*, 779 F.3d 34, 37 (1st Cir. 2015). First, a manufacturer can file a "Prior Approval Supplement" ("PAS") requesting revisions to the label. 21 C.F.R. § 314.70(b). That process requires FDA approval before implementation. Alternatively, a manufacturer can invoke what is called the "changes being effected" ("CBE") process to make an immediate label change in order to "add or strengthen a contraindication, warning, precaution, or adverse reaction," at the same time it submits a supplemental application to FDA, when "newly acquired information" reflects a "clinically significant hazard." 21 C.F.R. §§ 201.57(c)(6)(i), 314.70(c)(6)(iii).

The term "newly acquired information" means:

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

21 C.F.R. § 314.3(b). Of course, "FDA reviews CBE submissions and can reject label changes even after the manufacturer has made them." *Albrecht*, 139 S. Ct. at 1679. "But in the interim, the CBE regulation permits changes, so a drug

manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Id.*

C. Regulatory History of Zofran

1. 1988–1991: GSK Withholds Japanese Animal Studies That Revealed Teratogenicity When Seeking Initial FDA Approval for Zofran.

GSK sponsored seven full reproductive toxicology studies for Zofran: four animal studies in the United Kingdom (U.K.) and three in Japan through its affiliate Nippon Glaxo. PUB_000442.[4] Before each full study, GSK also sponsored a preliminary, dose-finding study. *Id.* While GSK disclosed to FDA the results of the four U.K. studies, which did not generally show evidence of teratogenicity (as they were insufficiently dosed, *see infra* pp. 36–42), GSK did not disclose the results of

[4] The full U.K. studies are:

R10590 (rats – oral);

R10937 (rats – intravenous);

L10649 (rabbits – oral); and

L10873 (rabbits – intravenous).

PUB_000446.

The full Japanese studies are:

100422 (rats – oral);

100424 (rats – IV); and

100441 (rabbits – oral).

PUB_000446.

three Japanese animal studies that did show evidence of teratogenicity.[5] PUB_000446–47.

> The three withheld Japanese animal studies showed the following results:
>
> Study 100423 reported an increase in embryofetal death in the 10 mg/kg intravenous Zofran-treated group of rats compared to untreated controls.
>
> Study 100424 reported increases in embryonic death and increased incidences of major external malformations in the 10 mg/kg intravenous Zofran-treated group of rats compared to controls and historical control data, including ventricular septal defects.
>
> Study 100441 reported an increase in some skeletal defects, among others in the 2.5 and 10 mg/kg oral Zofran-treated groups of rabbits compared to untreated controls.

PUB_000787. Plaintiffs' expert, Dr. Bengt Danielsson, a world-renowned teratologist, explains at length in his expert report that the Japanese animal studies were meaningfully different from the U.K. studies: unlike in the U.K. studies, the doses administered in the Japanese animal studies—while still generally insufficient to test Zofran's true teratogenic capability—provided sufficient exposure to show evidence of teratogenicity. PUB_000637. Dr. Danielsson also explains that the observed malformations from Zofran animal studies correlate with malformations seen in other similar-acting drugs (so-called "hERG-blocking-drugs") associated

[5] GSK submitted a translated version of study 100422 to FDA in 1997, PUB_004045, but failed to disclose a preliminary study, 100423, which also showed evidence of teratogenicity. PUB_000446–47.

with cardiac arrhythmia risk and also with observed malformations with Zofran in human epidemiology studies (in particular cardiovascular defects and orofacial clefts). PUB_000601–27. Dr. Danielsson published his review of this and other data, as well as his conclusions regarding Zofran's teratogenicity, in a well-respected, peer-reviewed journal, *Reproductive Toxicology*, in 2018. PUB_002753.

Because GSK had withheld this evidence of teratogenicity from FDA, the agency approved Zofran as a Pregnancy Category B drug. PUB_001077. Consequently, the approved labeling for Zofran stated:

> Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30mg/kg per day, respectively, and *have revealed no evidence of impaired fertility or harm to the fetus* due to ondansetron. . . .

PUB_001077 (emphasis added).

At the time Plaintiffs were prescribed Zofran, GSK's primary competition for anti-nausea drugs were Phenergan and Reglan, two drugs classified as Pregnancy Category C. GSK therefore took advantage of Zofran's Category B designation to aggressively market the drug to OB/GYNs to treat nausea and vomiting during pregnancy. UR_001200. [redacted]. UR_001176.

2. 1993: GSK Misleads FDA Regarding Japanese Studies in Annual Report.

In 1993, GSK submitted an "Annual Report" for Zofran to FDA, as required under 21 C.F.R. § 312.33. PUB_003835. In this Report, for the first time, GSK alerted FDA to the existence of the Japanese animal studies, but only by name and study number. PUB_003873. GSK told the agency that these studies were not significant: the disclosure was made under a sub-heading entitled "Studies performed specifically to satisfy Japanese regulatory requirements. These studies are either repetitive or *provide no new significant safety information*." PUB_003872–73. (emphasis added). GSK did not provide the studies themselves to FDA. *See* PUB_003825–80.

3. 1994–2018: Despite FDA Requests, GSK Continues to Withhold Japanese Animal Studies.

a. 2010: FDA Asks GSK to Review Zofran's Safety in Pregnancy.

In late 2010, FDA became concerned about Zofran's use by pregnant women. The agency wrote GSK to request information on this use:

> We note that ondansetron is widely used for treatment of nausea and vomiting during pregnancy. Please review and analyze available published and unpublished literature on the use of ondansetron during pregnancy and lactation, with a focus on the presence or absence of

> adverse pregnancy and/or neonatal outcomes. Please include an assessment of the strengths and limitations of the data.

PUB_001140. FDA asked GSK to submit proposed labeling revisions if GSK concluded changes were necessary to "furnish adequate information for the safe use of this drug." *Id*.

GSK responded in April 2011:

> GlaxoSmithKline does not believe there is sufficient evidence to warrant a change in the US Package Insert. GlaxoSmithKline believes that the text in the 'Pregnancy and lactation' section of the USPI accurately reflects the available data and provides a clear message to the prescriber that the safety of ondansetron for use in human pregnancy has not been established and is not recommended. Importantly, the current verbiage in the label clearly reflects the language mandated by 21 CFR 201.57, (6)(i)(b) and 21 CFR 201.57 (8)(ii).

PUB_001144. GSK neither disclosed nor made any mention of the withheld Japanese animal studies. Based on GSK's response, FDA took no further action. PUB_001169.

b. 2013: Reichmann Citizen Petition

In early 2013, an individual, James Reichmann, submitted a Citizen Petition to FDA regarding Zofran. PUB_001174. Reichmann requested that the FDA:

> 1. Reclassify the drug ondansetron (Zofran) from pregnancy category B to category C, D, or X after evaluation of "new safety information".
>
> 2. Notify OB/GYNs that there is insufficient scientifically acceptable evidence that ondansetron is associated with

> improved treatment outcomes and may lead to adverse maternal and fetal events or outcomes. . . .

PUB_001175. Reichmann referenced human observational studies to allege there was a lack of efficacy data for Zofran's use in pregnancy, a lack of safety data, and that certain heart disturbances may occur with use of Zofran. PUB_001174–78. Reichmann did not reference the Japanese animal studies. Nor, despite its awareness of the Reichmann Petition, did GSK respond to the petition or submit the Japanese animal studies to FDA. *See* UR_000560.

FDA denied Reichmann's Citizen Petition in October 2015. PUB_001188–1207. In its response, FDA relied in part on the U.K. animal data GSK had previously provided to justify Zofran's pregnancy classification:

> In 1989, Tucker et al. published the results of a preclinical safety evaluation of ondansetron. This evaluation was submitted in support of the 1991 approval of Zofran, and certain information from it is included in labeling for Zofran drug products.
>
> *The reproduction studies conducted as part of the safety evaluation are relevant to this Petition.* Tucker et al. described results from reproduction studies performed in pregnant rats and rabbits given ondansetron IV doses up to 4 mg/kg per day, which is approximately 1.5 to 3 times the recommended human IV dose of 0.15 mg/kg given three times daily. These studies did not show any evidence of impaired fertility or harm to the fetus due to ondansetron. *Ondansetron was classified as pregnancy category B based on these negative findings* . . . .

PUB_001199 (emphasis added) (footnotes omitted).

c. 2014: FDA Asks GSK for "Full Details" of Reproductive Studies

In early 2014, GSK submitted changes to Zofran's labeling to comport with a new FDA labeling rule, which required certain modifications to the label's layout to highlight commonly referenced information and improve readability. PUB_003121; PUB_003128. One of GSK's proposed changes noted that the U.K. animal studies had been conducted at "approximately 6 and 24 times the maximum human oral dose of 24 mg/day, based on body surface area." UR_02573.

While considering GSK's application, FDA asked GSK to "*please provide full details of animal reproduction studies*" of Zofran. UR_000501 (emphasis added). GSK responded in March 2015, stating that it was providing "full details of animal reproduction studies as requested." UR_000528. However, GSK's response merely described the same U.K. animal studies that had been submitted with its initial application back in 1989; GSK made no reference to—much less provided "full details" of—the withheld Japanese animal studies. *Id*.

d. 2015: Novartis Acquires Zofran and Seeks to Comply with New Pregnancy Labeling Rules

After Novartis acquired Zofran from GSK in 2015, it assumed responsibility for updating the labeling to comply with the new PLLR approach. PUB_000493. Based on the available human epidemiological data, Novartis proposed new labeling to FDA that stated "It is *possible* that ZOFRAN can cause harm to the fetus when

administered to a pregnant woman." PUB_001223 (emphasis added). Novartis's proposal did not make reference to the Japanese animal study data, which GSK had not provided to Novartis. *Id.*

The human epidemiological data that Novartis relied upon, which it described as "[redacted]," was underpowered[6] to detect Zofran's true teratogenicity. UR_000169. Well-powered epidemiology studies of birth defects usually require many thousands of subjects to yield statistically significant results. PUB_002785. The human studies that Novartis relied upon, by contrast, were based on sample sizes too small to detect specific birth defects (the number of pregnant women exposed to ondansetron in those studies ranged from 65 to 1349). PUB_000140–43. GSK's own epidemiology expert, Dr. Kimmel, wrote that "any specific birth defect is rare, occurring in 1 per 1,000 births" (specifically mentioning oral clefts as an example) and one would need "over 20,000" women exposed to a drug during pregnancy "to detect a doubling of risk," and "a far larger sample size to rule out a doubling of risk." PUB_012350–53.[7]

[6] "[A] large enough sample of individuals must be studied if the study is to identify a relationship between exposure to an agent and disease that truly exists." PUB_012197. "The power of a study is the probability of finding a statistically significant association of a given magnitude (if it exists) in light of the sample sizes used in the study." PUB_012203.

[7] Given this fact, leading scientists have rejected the requirement of multiple consistent epidemiology studies as a *sine qua non* to causal inference. PUB_012354–60. In fact, a study of seventeen teratogenic drugs identified from 1952 through 2008

FDA declined to add Novartis's proposed language regarding possible fetal harm, because "the available human data do not support a clear conclusion on an increased risk of major congenital malformation." PUB_001252. FDA expressly relied on the *absence* of evidence of teratogenicity in Zofran animal studies to support its conclusion, noting that "there is no evidence, *nonclinical* or mechanism of action, that raises concerns for adverse fetal outcomes with Zofran." PUB_001353 (emphasis added).[8] Of course, FDA remained unaware of the Japanese study data.

4. 2019–2021: GSK Finally Gives FDA the Japanese Animal Studies, but the Agency Has No Cause to Consider Them.

a. GSK's Citizen Petition

On November 1, 2019, on the eve of oral argument on its renewed summary judgment motion, GSK filed its own Citizen Petition with FDA, asking the agency to "review four categories of information concerning the use of [Zofran] in pregnancy." PUB_007811–33. Specifically, GSK asked FDA to review information that Plaintiffs in this litigation had contended constituted material scientific evidence previously withheld by GSK, including the Japanese animal studies.[9] PUB_007816.

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reported only one drug for which epidemiology was listed as the sole method of initial detection of teratogenicity in humans. PUB_012355.

[8] "Nonclinical" studies include animal studies.

[9] On appeal, Plaintiffs focus on the Japanese animal studies as "newly acquired information" that would justify a labeling change. The three remaining categories (adverse event data, mechanism of action literature, and a small observational study known as "the Einarson study"), discussed in the record below, supplement and

And, for the first time, GSK provided the Japanese studies to FDA. PUB_007821–23.

GSK was aware of ongoing agency conversations with Novartis concerning the safety of Zofran's use in pregnancy based on newly emerging human epidemiological studies; GSK's petition therefore expressly asked FDA to *ignore* that new information, and instead "either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling" *solely* in light of the information submitted with the petition. PUB_007816. Plaintiffs opposed GSK's petition as an improper use of the Citizen Petition process. PUB_007853–58.

On January 15, 2021, FDA denied GSK's Citizen Petition. PUB_010468–83. FDA informed GSK: "your request . . . is denied *without comment on the relevance, if any, of this information to ondansetron product labeling*." PUB_010469 (emphasis added). FDA advised that it "ha[d] serious policy and administrative concerns about engaging in the review requested by the Petition," and "concluded that the limitations you have placed on your request render the question essentially hypothetical and therefore inappropriate for the citizen petition process." PUB_010482.

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bolster Plaintiffs' claim that Zofran is teratogenic, but Plaintiffs do not contend on this appeal that they were, by themselves, sufficient to preclude the district court's preemption finding.

b. Novartis's 2020 PAS Application

While GSK's petition was pending, Novartis again proposed labeling changes—and again, based *only* on new human epidemiological data that showed further evidence of Zofran's teratogenicity. UR_001661. Novartis sought to add, *inter alia*, a caution to Zofran's "Risk Summary" pregnancy subsection (§ 8.1) stating:

> In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy. Regarding cardiac malformation, the epidemiological studies showed conflicting results. . . . The use of ondansetron in pregnancy is not recommended.

UR_02544. In the Clinical Overview to its submission, [redacted] UR_02535. [redacted] *Id*.

Importantly, Novartis proposed no changes to the label's pregnancy risk summary section concerning animal studies or its animal data subpart within the pregnancy section. UR_02545. [redacted]. UR_02519. [redacted]

[redacted]." *Id.* Novartis therefore proposed no labeling changes concerning animal studies. UR_02545.

After a series of exchanges, FDA approved new labeling language in a modified PAS on April 29, 2021. PUB_011019. The agency did not permit Novartis to recommend against Zofran use during pregnancy generally, because the published human epidemiological studies "[redacted]." UR_002261. FDA did, however, permit Novartis to include a description of the results of the epidemiological studies that had found an association between ondansetron use and birth defects. PUB_011030. Specifically, the approved revised Zofran label states:

> Ondansetron exposure in utero has not been associated with overall major congenital malformations in aggregate analyses. One large retrospective cohort study examined 1970 women who received a prescription for ondansetron during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage, stillbirth, preterm delivery, infants of low birth weight, or infants small for gestational age.
>
> Two large retrospective cohort studies and one case-control study have assessed ondansetron exposure in the first trimester and risk of cardiovascular defects with inconsistent findings. Relative risks (RR) ranged from 0.97 (95% CI 0.86 to 1.10) to 1.62 (95% CI 1.04, 2.54). A subset analysis in one of the cohort studies observed that ondansetron was specifically associated with cardiac septal defects (RR 2.05, 95% CI 1.19, 3.28); however, this association was not confirmed in other studies.

> Several studies have assessed ondansetron and the risk of oral clefts with inconsistent findings. A retrospective cohort study of 1.8 million pregnancies in the US Medicaid Database showed an increased risk of oral clefts among 88,467 pregnancies in which oral ondansetron was prescribed in the first trimester (RR 1.24, 95% CI 1.03, 1.48), but no such association was reported with intravenous ondansetron in 23,866 pregnancies (RR 0.95, 95% CI 0.63, 1.43). In the subgroup of women who received both forms of administration, the RR was 1.07 (95% CI 0.59, 1.93). Two case-control studies, using data from birth defects surveillance programs, reported conflicting associations between maternal use of ondansetron and isolated cleft palate (OR 1.6 [95% CI 1.1, 2.3] and 0.5 [95% CI 0.3, 1.0]). It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6th and 9th weeks of pregnancy).

PUB_011030–31. Because Novartis had not sought any changes to the label concerning animal studies, FDA did not make any changes to those sections (apart from one minor grammatical correction to one version of the label). PUB_011016.

There is no direct evidence that FDA reviewed or analyzed the Japanese animal studies in the course of considering this latest labeling change to Zofran. Indeed, there is no evidence that FDA ever considered the Japanese animal studies in the entire regulatory history of Zofran.

II. PROCEDURAL HISTORY

The JPML established the *In re Zofran (Ondansetron) Products Liability Litigation* MDL in October 2015 and assigned it to the District of Massachusetts. PUB_000001. Less than two months later, GSK moved to dismiss all of Plaintiffs' claims on preemption grounds. PUB_000006. The district court denied this motion,

writing: "[P]laintiffs are entitled to an opportunity to develop the record as to how the FDA would have responded to a proposal had GSK submitted one." PUB_000180.

In July 2018, GSK moved for summary judgment based on federal preemption. PUB_000082. The district court again denied GSK's motion. PUB_000404. The district court ruled that there was "at a minimum" a genuine disputed issue of material fact as to whether FDA would have approved a birth defect warning for Zofran if it had been provided with material scientific information that GSK had withheld from the agency, including the Japanese animal studies. PUB_000397. The district court applied the same "fully informed" standard later adopted by the Supreme Court in *Albrecht* when it wrote: "GSK has to show that the FDA was fully informed as to the relevant science, and that any alleged omission or failure to disclose was not material." PUB_000393. With specific regard to the Japanese animal studies, the district court stated: "It is unclear how the Court could conclude on the present record that the 'list' and 'summary' provided to the FDA [in 1993] were complete and accurate." PUB_000395.[10] Under the then-existing legal framework, the district court concluded that summary judgment was improper

[10] Concerning the question whether the withheld Japanese animal studies satisfied the regulatory standard for "newly acquired information," as Plaintiffs' experts said they did, the Court noted: "GSK has submitted no expert or other affidavit in response." PUB_000395.

because "clear evidence" preemption was a factual issue that must be resolved by a jury. PUB_000387. GSK moved for reconsideration, which the district court denied. PUB_000405.

In May 2019, the Supreme Court decided *Albrecht*, holding among other things "that a judge, not the jury, must decide the pre-emption question." 139 S. Ct. at 1676. In response to that ruling, the district court vacated "relevant portions" of its summary judgment order, including its discussion of whether preemption presented a question of fact for a jury and its related conclusions, and permitted GSK to file a renewed summary judgment motion. PUB_000421–22.

In July 2019, GSK renewed its motion for summary judgment on preemption grounds and submitted four new witness declarations. PUB_007268–69. The district court struck three of those declarations as untimely and without justification.[11] PUB_007296–97. GSK then filed an amended renewed motion, which removed reference to those declarations, and is the operative motion upon which the district court granted summary judgment.

[11] The district court struck the declarations of GSK's three expert witnesses: (1) Dr. Dena Hixon (regulatory); (2) Dr. Gary Shaw (epidemiology); and (3) Dr. Patrick Wier (reproductive toxicology), because they had been submitted well after the expert disclosure deadline; however, the court declined to strike testimony from a fact witness, GSK employee Luise Rogg. PUB_007268–97.

Just days before oral argument, GSK filed its Citizen Petition asking FDA to consider Plaintiffs' evidence of newly acquired information. PUB_007811. The parties submitted additional briefing regarding the propriety and effects of GSK's Citizen Petition, as well as supplemental briefing related to FDA action on Novartis's subsequent labeling PAS. *See, e.g.*, PUB_007853.

On June 1, 2021, the district court granted GSK's motion. *See* Addendum. The court assumed, without deciding, that the Japanese animal studies "constituted 'newly acquired information' as defined by the CBE regulations, and therefore GSK could have attempted to amend the Zofran label unilaterally at one or more points during the period it owned the rights to the drug." Addendum 54. The court also did not dispute that FDA had not been "fully informed" of all relevant scientific information prior to the 2019 GSK Citizen Petition. Addendum 57. Because, however, there was no dispute that the agency had been given all of the withheld "newly acquired information" in connection with that petition, the district court concluded that FDA was "fully informed" of all newly acquired information by the time it considered the 2020 Novartis PAS. Addendum 57.

The district court ruled that FDA's actions on that application did have preemptive effect. The court reasoned, inaccurately, that FDA had "approved a label that contains language that is directly contrary to the language proposed by plaintiffs." Addendum 59. As to Plaintiffs' argument that FDA's actions on

Novartis's PAS could not be preemptive, because Novartis had not sought any changes to the label related to animal studies, the district court responded:

> [Plaintiffs' argument] assumes that the FDA was not following the statutory requirement that it consider 'all' relevant information in evaluating the PAS. In this context, at least, the Court will not assume that the FDA failed to perform, in fact blatantly ignored, its statutory duties to review and monitor the drug for human safety. Accepting plaintiffs' argument would suggest that the FDA conducted a narrow and myopic review of the safety of the drug, considering only what Novartis asked it to consider, and that it turned a blind eye to evidence that Zofran causes birth defects. That is highly unlikely, to say the least.

Addendum 61. Upon that order, Plaintiffs appeal.

SUMMARY OF THE ARGUMENT

The district court's ruling must be reversed. *Levine* and *Albrecht* articulate a test for impossibility preemption that GSK simply has not met here. Because the CBE regulation permits a manufacturer to modify a warning without prior FDA approval in "virtually all situations in which new information indicates new or greater risks," *In re Celexa & Lexapro*, 779 F.3d at 41, "a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both," *Albrecht*, 139 S. Ct. at 1679. Under the Supreme Court's precedent,

> showing that federal law prohibited the drug manufacturer from adding a warning that would satisfy state law requires the drug manufacturer to show that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning.

Id. at 1678. GSK has not made that showing here.

Plaintiffs' argument proceeds in three steps. First, the Japanese animal studies that GSK withheld from FDA until 2019 are "newly acquired information," *i.e.*, "data, analyses, or other information not previously submitted to the Agency . . . [that] reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA;" they would have supported a CBE label change from Pregnancy Category B to Pregnancy Category C, and thereby warned prescribers and pregnant mothers that animal studies showed harm to the fetus when

Zofran was ingested during pregnancy. The Japanese animal studies reveal evidence of Zofran's teratogenicity that the submitted U.K. studies did not. As explained by Plaintiffs' expert teratologist, Dr. Bengt Danielsson, unlike the U.K. studies, which were consistently underdosed, at least some of the subgroups in the Japanese studies were dosed at levels comparable to human exposure, and those subgroups showed evidence of teratogenic effect. Plaintiffs' regulatory expert Dr. Brian Harvey, the former Director of FDA's Division of Gastroenterology Products, and the only regulatory expert in this case, opined that "[t]he findings of the Japanese animal studies would have supported a label change through the CBE process at any point in time."

Second, as the district court appears to have recognized, because GSK withheld the Japanese animal studies from FDA until 2019, no regulatory action taken by the agency prior to that time—including the entire time that GSK held the rights to Zofran—can have preemptive effect. GSK cannot show, during that period, that "it fully informed the FDA of the justifications for the warning required by state law." *Albrecht*, 139 S. Ct. at 1678.

Third, no regulatory action that has occurred since 2019, satisfies the second prong of *Albrecht*'s preemption test, that the FDA, having been fully informed, "in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Id*. Although GSK did ask FDA to opine on

the significance of the Japanese animal studies for Zofran's pregnancy labeling in its 2019 Citizen Petition, FDA expressly denied that petition "without comment on the relevance, if any, of this information to ondansetron product labeling." And, when Novartis—the current label-holder for Zofran—sought to add a pregnancy warning in 2020 based on new human epidemiological data, the company did not ask FDA to consider the Japanese animal data (indeed, it told the agency that the studies did not reveal evidence of teratogenicity), and FDA said nothing about the Japanese studies in acting on Novartis's request.

These are the only two "agency action[s] carrying the force of law" FDA has taken with regard to Zofran's label since it received the Japanese animal studies, yet neither "communicate[s] its disapproval of a warning" based on that data. *Albrecht*, 139 S. Ct. at 1679. That should be the end of the matter. Anything else is conjecture about what FDA would have done if GSK—or Novartis—had asked for a label change based on the Japanese studies. But such "hypothetical agency action is not 'Law,'" *id.* at 1683 (Thomas, J., concurring); as the Supreme Court has instructed: "the 'possibility of impossibility [is] not enough.'" *Id.* at 1678-79 (alteration in original) (quoting *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 624 n.8 (2011)). The district court's

> belief that the FDA would have eventually rejected a CBE application does not make an earlier CBE change impossible. . . . The very point of the CBE process is that a manufacturer can "unilaterally" make a

> labeling change that does not violate other federal law, at least until the FDA rules on its application.

Id. at 1683 (Thomas, J., concurring) (internal citations omitted).

For each of these reasons, this Court should reverse the district court's grant of summary judgment based on preemption.

STANDARD OF REVIEW

"We review the district court's grant of a summary judgment motion *de novo*." *Sparks v. Fid. Nat'l Title Ins. Co.*, 294 F.3d 259, 265 (1st Cir. 2002). "In deciding a summary judgment motion, we must view the evidence in the light most favorable to the nonmoving party and must draw all reasonable inferences in the nonmoving party's favor." *Id.*

The Supreme Court decided in *Albrecht* that the question of "clear evidence" preemption is a legal one for the judge, not a jury. 139 S. Ct. at 1679. In this Circuit, such legal determinations are also reviewed *de novo*. *Spectrum Ne., LLC v. Frey*, 22 F.4th 287, 291 (1st Cir. 2022) ("We review a district court's legal conclusions de novo.")

Other circuit courts have reviewed impossibility preemption post-*Albrecht* under a *de novo* standard. *See, e.g., In re MDL 2700 Genentech Herceptin (Trastuzumab) Mktg. & Sales Prac. Litig.*, 960 F.3d 1210, 1224 (10th Cir. 2020) ("We ordinarily consider pre[-]emption as a legal issue subject to de novo review." (alteration in original)); *Knight v. Boehringer Ingelheim Pharms., Inc.*, 984 F.3d 329, 337 (4th Cir. 2021) ("Preemption is a question of law, which we review de novo."); *Hardeman v. Monsanto Co.*, 997 F.3d 941, 954 (9th Cir. 2021) ("Whether Hardeman's state claims are preempted is reviewed de novo.").

ARGUMENT

I. THE THREE JAPANESE ANIMAL STUDIES THAT GSK WITHHELD FROM FDA UNTIL 2019 CONSTITUTE "NEWLY ACQUIRED INFORMATION" THAT WOULD HAVE SUPPORTED A CBE LABELING CHANGE.

In its ruling, the district court "assume[d], without deciding, that the information at issue constituted 'newly acquired information' as defined by the CBE regulations, and that therefore GSK could have attempted to amend the Zofran label unilaterally at one or more points during the period it owned the rights to the drug." Addendum 54. That assumption was correct and should be affirmed by this Court.

As explained above, *supra* pp. 9–11, a drug manufacturer can invoke the CBE process to make an immediate, unilateral label change to add or strengthen a warning or precaution when it possesses "newly acquired information" that provides "reasonable evidence of a causal association" between the drug and a "clinically significant hazard"; "a causal relationship need not have been definitely established." 21 C.F.R. §§ 201.57(c)(6)(i), 314.70(c)(6)(iii). 21 C.F.R. § 314.3(b) defines "newly acquired information" to mean:

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

The Japanese animal studies that GSK withheld from FDA easily satisfy this definition, for at least three reasons: (1) they reveal evidence of teratogenicity that

the U.K. studies GSK provided did not; (2) although themselves flawed, they were meaningfully different from the U.K. studies; and (3) Plaintiffs' regulatory expert Dr. Brian Harvey—the former Director of FDA's Division of Gastroenterology Products, with responsibility over Zofran labeling—opined that the studies constituted "newly acquired information." Legal precedent also supports the conclusion that the Japanese animal studies are newly acquired information.

A. The Three Withheld Japanese Animal Studies Revealed Evidence of Teratogenicity That the U.K. Studies Did Not.

GSK disclosed to FDA the results of four U.K. animal studies, which did not show evidence of teratogenicity (because they were insufficiently dosed, as explained below). However, GSK failed to disclose the results of three Japanese studies, each of which showed evidence of teratogenicity.[12] These studies revealed:

> An *increase in embryofetal death* in the 10 mg/kg intravenous Zofran-treated group of rats compared to untreated controls. (No. 100423)
>
> *Increases in embryonic death* and *increased incidences of major external malformations* in the 10 mg/kg intravenous Zofran-treated group of rats compared to controls and historical control data, *including ventricular septal defects* [heart defects] among others. (No. 100424)

[12] Until 2019, GSK had only informed FDA of the existence of these studies in an annual report, characterizing them as "either repetitive or provide no new significant safety information." PUB_003872–73.

> An *increase in some skeletal defects*, among others, in the 2.5 and 10 mg/kg oral Zofran-treated groups of rabbits compared to untreated controls. (No. 100441)

PUB_000787 (emphases added).

These results—standing alone—are newly acquired information that would justify a labeling change, as they are reasonable evidence of a causal association between Zofran and birth defects; they reveal risks of a different type and greater severity and frequency than the disclosed U.K. animal studies. As Plaintiffs' expert Dr. Danielsson wrote regarding these studies: "at dose levels in rats and rabbits appropriately exceeding human therapeutic exposure for short periods, teratogenicity of ondansetron was observed." PUB_000656. Dr. Danielsson continued: "The causal relationship of ondansetron to the malformations seen in treated animals in the Glaxo studies is also strengthened in view of lack of malformations in concurrent controls, reproducibility of cardiovascular defects in the studies, and that malformations were only noticed in the studies with highest exposures." PUB_000648.

According to FDA: "Warnings about a drug's risks in pregnancy could be based entirely on animal data." PUB_012092. Recall that, at the time virtually all Plaintiffs used Zofran, the distinction between Pregnancy Categories B and C turned on whether pre-clinical animal studies had revealed evidence that the drug was teratogenic, as the withheld studies do. Yet GSK never disclosed the results of these

studies to FDA when it was the label-holder for Zofran, not even when FDA conducted a review of Zofran's safety for use in pregnancy in 2010, nor when FDA asked GSK for "full details of [Zofran's] animal reproduction studies" in 2014. UR_000501. Because these studies reveal "reasonable evidence of a causal association" between Zofran and birth defects, they are "newly acquired information" that would have justified a CBE labeling change.

B. The Withheld Japanese Studies Meaningfully Differ from the U.K. Studies Because, at Least at Their Higher Dosing Levels, They Approached Levels of Human Exposure Sufficient to Reveal Evidence of Zofran's Teratogenicity.

As explained in the expert report of Dr. Danielsson, 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. PUB_000647 ("The low exposures of ondansetron in the Glaxo animal studies did not meet regulatory expectations and industry standards today, especially for a drug which can be expected to be or is used widely in pregnancy."). By contrast, the Japanese studies—while also not generally dosed to match human exposure—were dosed at levels higher than the U.K. studies, with some approaching human exposure levels, and yielded some evidence of teratogenicity. PUB_000637.

To expand on this point, it is important to understand that there is a critical distinction between the *dose* of a drug given to an animal and the *exposure* achieved

in that animal, based on how that particular species absorbs, distributes, metabolizes and eliminates the chemical. UR_02313. According to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),[13] information on systemic exposure of pregnant animals is "essential for the interpretation of study results, and thus to assess human safety." PUB_012348. An evaluation of animal teratology studies should therefore compare exposure levels in the tested animals in relation to the highest proposed exposure in humans. PUB_0121157. As Dr. Danielsson explained: "According to current guidelines on teratology testing, it is essential to select dose levels and animal models in teratology studies which result in both significantly higher total exposure per day (AUC), and higher maximal concentrations (Cmax) than human therapeutic exposures/concentrations, in order to detect teratogenic potential in humans." PUB_000623. "Only at higher exposures than in humans (both regarding Cmax and AUC) is it possible to fully characterize the drug's human teratogenic potential." PUB_000653.

Additionally, according to the ICH guidelines, "[t]he species used [in animal testing] should be well-characterized and relevant for detecting effects on the

[13] The ICH promulgates guidelines that "recommend international standards for, and promote harmonization of, the assessment of nonclinical developmental and reproductive toxicity (DART) testing necessary to support human clinical trials and marketing authorization for pharmaceuticals." PUB_012228.

endpoints in a particular study (e.g., with respect to health, fertility, fecundity, background rates of malformation and embryo-fetal death, etc.)." PUB_001662. For this reason, the specific species of subject animals selected for reproductive toxicity studies are bred to reduce the background rate of abnormalities in order to isolate the true teratogenic capability of a drug. *See* PUB_001663. Thus, unlike in human epidemiological studies, abnormalities observed in animal studies are much more likely to have been caused by the tested drug.

As Dr. Danielsson observed, in Zofran animal teratology studies where the animals were properly exposed at levels relevant to human exposure, the animals had increased incidences of malformations and deaths compared to controls. PUB_000638. By contrast, studies that did not find evidence of birth effects under-dosed the animals:

> [I]t is of major importance and stressed in guidelines, to obtain exposures (both regarding Cmax and AUC), in the middle, and especially the high dose, several times higher in animal teratology studies than human therapeutic exposures. The low exposures of ondansetron in the Glaxo animal studies did not meet regulatory expectations and industry standards today, especially for a drug which can be expected to be or is used widely in pregnancy. Several dose levels used in conducted teratology studies resulted in lower exposures than what was observed in a woman administered an 8 mg tablet of

> ondansetron in early pregnancy, both regarding systemic exposure (AUC) and peak concentrations (Cmax).

PUB_000647–48. According to Dr. Danielsson, GSK's failure to adequately dose the animals explains why most reportedly "exposed" animals in GSK's studies did not have malformations or die. *See* PUB_000633; PUB_000653.

GSK consistently failed to present any data to FDA concerning either peak concentrations or systemic exposure in its Zofran teratology studies. PUB_000633; UR_02440.[14] Quite literally, it was GSK company policy *not* to study Zofran's true teratogenicity. GSK's Director of Oncology North American Affairs wrote in 2002: "[redacted]." Instead, GSK chose to bury its head in the sand.

Dr. Danielsson did what GSK did not: he compared animal and human Zofran exposures and demonstrated this exposure discrepancy. PUB_000632. He then evaluated the findings of malformations and deaths in the Zofran-treated groups compared to controls in light of the essential exposure data and informed by knowledge of typical malformations that were induced by other hERG-blocking drugs.[15] PUB_000646. As explained in greater detail below, his evaluation showed

[14] In one U.K. study, Study R10615, GSK collected and presented exposure data, which confirms that GSK had the ability to do so, but chose not to. PUB_006165.

[15] The term hERG stands for "human ether-a-go-go-related gene." PUB_000628. The hERG potassium channels are critical determinants of cardiac repolarization. *Id.*

that the observed malformations in certain Zofran-treated groups in the studies correlated well with the exposures that met or slightly exceeded human exposure (none significantly exceeded it) and fit the pattern of malformations and deaths observed with other hERG-blocking drugs. PUB_000638.

1. Most of GSK's Reproductive Toxicity Studies Were Insufficiently Dosed to Detect Teratogenicity in Humans.

As Dr. Danielsson showed, the systemic drug exposures of the rats exposed prenatally to Zofran at all dose levels except the highest intravenous dose in Study 100424, measured by AUC, were all *less* than the exposure reported in a pregnant adult woman treated with the recommended dosage of Zofran at 8 mg three times daily. PUB_000636. For U.K. rat study R10590—an oral dose study—all Zofran doses resulted in exposures that fell below human exposure. *Id.* U.K. rabbit study L10649 and Japanese rabbit study 100441—both oral dose studies—most likely also resulted in exposures below human exposure at all doses levels, based on rabbits' rapid metabolism and elimination of ondansetron compared to humans.

Zofran is a hERG-blocking drug. *Id.* There is considerable evidence that the hERG channel is an important target for induction of teratogenicity in animals for other potent hERG-blocking drugs, which like ondansetron, have an established risk for cardiac arrhythmia when used as recommended. PUB_000598.

PUB_000656. Similarly, in Study R10937, the high intravenous dose of 4 mg/kg in rats resulted in only roughly 76% of the human exposure. PUB_000636.[16]

The low dose used in an animal teratology study should generally achieve an exposure that is a low multiple (e.g., 1 to 5-fold) of the human exposure at the MRHD [maximum recommended human dose]." PUB_001670. Under ICH guidelines, therefore, the results of these studies, which in general did not report biologically significant increases in the incidence of malformations in Zofran-treated groups, do not permit an inference that Zofran does not cause malformations or death in humans.

Further, for all of the Zofran rat teratology studies, *none* of the low-dose groups achieved exposure equal to human exposure. PUB_000636. In Japanese Study 100422, the high-dose (40 mg/kg) group achieved an exposure less than two times greater than the human exposure reported in early pregnancy at one 8 mg tablet taken once daily. *Id*. Nevertheless, major cardiovascular defects including a *ventricular septal defect* in the heart—one of the injuries alleged by many Plaintiffs—and situs inversus totalis (heart on wrong side of body) were observed in

[16] Even so, this high-dose group reported increased incidences of cardiovascular malformations, such as abnormal subclavian artery and enlarged atrium. PUB_000647. The low-dose group, at only 40% of the once daily human exposure, resulted in an increased incidence of cleft palate versus concurrent controls. PUB_000646.

the high dose group but not in the concurrent, unexposed control group. PUB_000641.

In Japanese Study 100424, the high intravenous dose of 10mg/kg resulted in an exposure roughly 6.6 times higher than human exposure. PUB_000636. This group experienced an increased incidence of cardiovascular defects compared to concurrent, untreated controls and when compared to Study 100422, which achieved lower exposure levels. PUB_000642. In Study 100424, the increased incidence of cardiovascular defects included *two ventricular septal defects*—again, one of the injuries that many Plaintiffs allege—as well as dilation of renal pelvis and increased incidences of skeletal anomalies. *Id*.

2. Under ICH Standards, the Japanese Animal Studies Showed Evidence of Teratogenicity.

The vast majority of teratogenic effects seen in Zofran-treated groups—such as the two ventricular septal defects seen in the undisclosed Japanese Study 100424, the increase in embryofetal death seen in the undisclosed Japanese Study 100423, and the increase in skeletal defects seen in the undisclosed Japanese Study 100441—occurred at exposures at or near the human exposure with a once-daily 8 mg tablet of Zofran (the recommended daily dose in the label is 8 mg *three times* daily). PUB_000636; PUB_000651. The teratogenic effects reported in the Zofran treated groups thus present a significant "increased concern for reproductive . . . toxicity in humans." PUB_001676.

Additionally, according to the ICH, as set forth in Dr. Danielsson's report, if similar malformations are observed in two mammalian species, known as "cross-species concordance," this is strong supporting evidence for teratogenicity in humans. PUB_000655; PUB_001559. Here, multiple defects, including both cardiovascular septal defects and cleft palate defects, were reported in both the adequately dosed Zofran-treated animal groups and in the human epidemiology studies.

Moreover, as Dr. Danielsson found, consistent with ICH S5 (R3), which directs experts to consider available data on "related compounds," the malformations observed in the Zofran-treated groups were the same malformations reported with other hERG-blocking drugs. PUB_000655. This similarity also supports the conclusion that Zofran is teratogenic: "Knowledge of the mechanism of action may help to determine whether a particular exposure is likely to have caused an infant's birth defects." PUB_000598–99.

In sum, all of this evidence—the results of the Japanese animal studies, the insufficient dosing and exposure used in GSK's animal studies, and the analyses of those studies by Plaintiffs' expert teratologist Dr. Danielsson under ICH guidelines—supports the conclusion that the withheld Japanese animal studies revealed risks of a different type or greater severity or frequency than previously

included in submission to FDA and thus constituted newly acquired evidence that could have supported a CBE label change.

C. Plaintiffs' Regulatory Expert Dr. Brian Harvey Opined that the Japanese Animal Studies Would Have Been Material and Showed Evidence of Risk Not Previously Submitted to FDA.

Plaintiffs' regulatory expert Brian E. Harvey M.D., Ph.D., who served as Director of the Division of Gastroenterology Products at FDA from 2005–2007, opined: "As the former Division Director with responsibility for regulating Zofran, the omitted information was material to me and based on my experience would have been material to a reasonable FDA official performing the same regulatory functions." PUB_000751–52. As Dr. Harvey's report states:

> FDA relies upon the drug sponsor to provide the agency with complete and accurate information, including at initial drug approval stage when there is often little published literature on the drug. [T]he agency requires the drug sponsor to include "studies of the effects of the drug on reproduction and on the developing fetus." To the extent any of the results of these studies showed adverse effects in the drug group that were not seen in the control group, regulatory standards required that GSK submit those studies to FDA."

PUB_000799; PUB_000800.

Dr. Harvey continued:

> The fact that there were 3 VSDs across 4 of the Japanese animal studies, with 2 VSDs in one study and 1 VSD in another study, FDA would have considered that evidence of a possible association. . . . Based upon my agency experience, had GSK done so, FDA would have taken into consideration all seven reproductive toxicology animal

> studies including the findings of evidence of developmental teratogenicity."

PUB_000799; PUB_000801 (referring to the two ventricular septal defects seen in study 100424 and one seen in study 100422). Given all this, according to Dr. Harvey: "A new analysis of the Japanese animal studies would have been considered 'newly acquired' information under FDA Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices and would have supported a label change under CBE." PUB_000840. "The findings of the Japanese animal studies would have supported a label change through the CBE process at any point in time . . . ." *Id.*

GSK, by contrast, has no sworn expert testimony to contradict Dr. Harvey's regulatory opinion that the Japanese animal studies would have been material to FDA's reviews of Zofran's labeling and reflect a type or degree of risk previously unknown to FDA. Thus, Dr. Harvey, uniquely qualified to offer insight into the import of the Japanese animal studies, provides unrebutted expert testimony to further support the conclusion that these studies constituted "newly acquired information" that would have supported a CBE labeling change.

D. Legal Precedent Also Supports the Conclusion that the Japanese Animal Studies Constitute Newly Acquired Information.

The plaintiffs in *Levine*—who asserted that Wyeth failed to warn of the risk of amputation when injected with its drug Phenergan—survived preemption by

presenting "at least 20 reports" of amputations connected to the "IV-push method" that could have constituted newly acquired evidence supporting a label change. 555 U.S. at 562–64. The Court wrote: "Wyeth could have analyzed the accumulating data and added a stronger warning about IV-push administration of the drug." *Id.* at 570. Since there was no clear evidence that FDA would have rejected a Wyeth-initiated label change supported by this additional safety information, the Supreme Court could not find it actually impossible for Wyeth to comply with its state law duty to strengthen the label. *Id.* at 572-73.

Similarly, post-*Albrecht*, the plaintiffs in *In re Taxotere (Docetaxel) Products Liability Litigation* alleged that drug manufacturer Sanofi failed to warn of the risk of permanent alopecia (hair loss) with the use of its drug, Taxotere. 508 F. Supp. 3d 71, 84 (E.D. La. 2020). Plaintiffs offered, among other "newly acquired information," a study conducted by an oncologist that showed an increased risk of permanent alopecia ("the Sedlacek presentation"). *Id.* Sanofi argued that this work could not constitute "newly acquired information" because previously submitted data had also indicated some risk of permanent alopecia. *Id.* Sanofi argued that "[t]his study revealed nothing the FDA did not already know. *Id.*

The court rejected this argument: It was not enough for Sanofi to show that similar safety information had been submitted to FDA. *Id.* at 84–85. "Sanofi is attempting to shift the responsibility of analyzing these reports to the FDA," when

"the Supreme Court makes clear that a manufacturer must analyze the accumulating data—including *any pertinent data that predated supplemental applications*—for the FDA." *Id.* at 82, 85 (emphasis added).[17] "Considering the limitations of the data Sanofi provided to the FDA in 2004, the Sedlacek presentation, which centered around the risk of persistent alopecia, would have 'reveal[ed] risks of a different type or greater severity or frequency than previously included in submission to the FDA' . . . [and], therefore, constituted 'newly acquired information,' . . . to support a CBE change." *Id.* at 85 (first alteration in original).

As this Court explained in *In re Celexa and Lexapro*, the line *Levine* drew between labeling changes that can be made by CBE and those that cannot "makes

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[17] The *Taxotere* court also noted that internal documents showed Sanofi, just like GSK, *see supra* p. 39, avoided studying whether there was an association between its drug and the adverse effect at issue:

> The evidence shows that in 2006, a physician asked Sanofi "if there was any documentation/knowledge about the reversibility of alopecia after Taxotere treatment (e.g., expected time frame)." He noted that his patient had suffered alopecia since 2004. In Sanofi's internal communications about this question, one of Sanofi's Global Safety Officers writes: "Only peripheral knowledge. I know that there were some irreversible cases of alopecia as documented in the clinical trials." Rather than suggesting an investigation, however, she writes this: "This is the kind of thing that a noncompany physician would review in their practice and possibly report in the literature--however, I am NOT advising a lit search for this topic!" This evidence suggests that Sanofi chose to ignore the accumulating data rather than investigate and analyze it.

508 F. Supp. 3rd at 84 (footnote call numbers omitted).

some pragmatic sense": "By hinging preemption on the availability of that procedure . . . , [*Levine*] effectively reserves the launch of new drugs to the expertise of the FDA, but then preserves a wide scope for the states in requiring manufacturers to respond to *information not considered by the FDA*." *Id.* at 41 (emphasis added).

As in *Taxotere*, it is not enough for GSK to offer that FDA already had *some* data related to Zofran's potential for teratogenicity and unilaterally deem that the Japanese animal studies were repetitive of information FDA already had. Like the Sedlacek presentation, the undisclosed Japanese animal studies would have "reveal[ed] risks of a different type or greater severity or frequency than previously included in submission to the FDA," and thus supported a CBE labeling change from Pregnancy Category B to C.

As the Supreme Court has instructed, FDA regulations define newly acquired information to include data that, although not "new" in time, may still have significance: "The rule accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments." *Levine*, 555 U.S. at 569. As Dr. Harvey opines, "when there is preliminary evidence of teratogenic risk in animal studies and a scientific basis for mechanism of action, the presence of birth defects in case studies, published literature and adverse events becomes more concerning and increases support for the causal connection to the use of the drug in pregnancy." PUB_000843.

Thus, as the district court correctly assumed, Addendum 54, the Japanese animal studies, which were withheld from FDA for almost three decades, are newly acquired information. They provided GSK, while it held the NDA for Zofran, with a basis to change Zofran's labeling to Pregnancy Category C unilaterally through the CBE process.

II. FDA'S PRE-2019 ACTIONS CANNOT JUSTIFY PREEMPTION BECAUSE FDA WAS NOT FULLY INFORMED OF THE TERATOGENICITY RISK SHOWN BY THE JAPANESE ANIMAL STUDIES.

Under *Albrecht*, impossibility preemption can only arise when the drug manufacturer can show the court that "it fully informed the FDA of the justifications for the warning required by state law" (and then, in turn, the FDA informs the manufacturer that it would not approve that warning). 139 S. Ct. at 1678. Here, there is no dispute that GSK did not provide the full Japanese animal studies to FDA until 2019, in connection with its unsuccessful Citizen Petition. PUB_007811. Thus, no action taken by FDA before 2019 can have preemptive effect.

In its 2019 summary judgment ruling, the district court correctly concluded that these facts required denial of GSK's preemption motion based on the pre-2019 regulatory record:

> The Court therefore cannot conclude, on the present record, that the Japanese animal studies were not 'newly acquired information' or would not have revealed 'risks of a different type or greater severity or frequency' than previously included in submissions to the FDA, or that there is 'clear evidence' that the FDA would have rejected plaintiffs'

> proposed label changes even if a more comprehensive disclosure had been made.

PUB_000397.

The court took a similar approach in its most recent ruling. Having "assumed" for purposes of this motion that the withheld Japanese animal studies "constituted 'newly acquired information' as defined by the CBE regulations," the district court simply skipped over all regulatory actions taken by FDA prior to the 2020 Novartis PAS application. Addendum 57. ("In summary, all of the information concerning the safety of Zofran that plaintiffs allege was withheld from the FDA had been provided to it by the time of the 2020 Novartis PAS."). The district court was undoubtedly correct to do so, as agency actions undertaken without full information cannot have preemptive effect. *See Albrecht*, 139 S. Ct. at 1678 ("[S]howing that federal law prohibited the drug manufacturer from adding a warning that would satisfy state law requires the drug manufacturer to show that it fully informed the FDA of the justifications for the warning required by state law.").

Substantial case law supports this conclusion that the pre-2019 regulatory record would not permit finding preemption because FDA was not "fully informed" of the justifications for the teratogenicity statement underpinning Plaintiffs' claims. In *Taxotere*, for example, the district court rejected the defendant manufacturer's argument that FDA would not have approved a permanent alopecia warning for its chemotherapy drug because the defendant could not show that FDA had received all

information material to the warning. 508 F. Supp. 3d at 86 ("The evidence shows that before Kahn was treated, Sanofi never 'fully informed' the FDA of the justifications for a warning regarding permanent alopecia."); *see also In re Avandia Mktg., Sales & Prods. Liab. Litig.*, 945 F.3d 749, 759 (3d Cir. 2019) ("[A] drug manufacturer must show that the FDA made a fully informed decision to reject a change to a drug's label in order to establish the 'demanding defense' of impossibility preemption."); *In re Testosterone Replacement Therapy Prods. Liab. Litig.*, 430 F. Supp. 3d 516, 531 (N.D. Ill. 2019) ("Martin's failure to warn claims, therefore, are not preempted . . . [when] Actavis does not offer evidence that it 'fully informed the FDA of the justifications for the warning[s]' that Martin contends were necessary." (third alteration in original)).

Similarly, in *Risperdal and Invega Cases*, 49 Cal. App. 5th 942 (2020), the court rejected the defendant manufacturer's argument that FDA would not have approved a gynecomastia warning for its antipsychotic drug because the defendant failed to disclose information from a statistical analysis of studies. The court found that "[i]t is undisputed that Janssen did not submit table 21 during the application or labeling process" and that this table provided information showing that "children who had elevated prolactin after taking risperidone for eight to 12 weeks were 2.8 times more likely to develop prolactin-related side effects, including gynecomastia." *Id.* at 958. In holding that the plaintiffs' claims were not preempted, the court

specifically rejected Janssen's argument for preemption based on FDA's denial of a citizen's petition on the same subject. *See id.* at 959 ("[T]he FDA did not have table 21 when it denied the citizens petition. Impossibility preemption requires the drug manufacturer to show that it fully informed the FDA. Janssen did not.").

Nor did GSK fully inform FDA here of information material to the teratogenicity risk when it withheld the Japanese animal studies for nearly three decades, from FDA's approval of Zofran in 1991 until 2019, long after GSK had sold the drug to Novartis. Because FDA was not fully informed of the teratogenicity risk before 2019, there is no basis for finding preemption based on any FDA action during this period.

III. NONE OF THE FDA'S ACTIONS POST-2019 CONSTITUTE CLEAR EVIDENCE THAT FDA WOULD HAVE REJECTED A STRONGER PREGNANCY WARNING CONCERNING THE ANIMAL STUDY DATA, BECAUSE FDA HAS NEVER EXPRESSLY REJECTED SUCH A WARNING, AND FDA DISAPPROVAL CANNOT BE INFERRED FROM AGENCY SILENCE.

Only in 2019 did GSK finally provide the Japanese animal studies, conducted thirty years earlier, to FDA as part of its improper Citizen Petition. PUB_007811. There is no dispute that, after that date, FDA had, at long last—and for the first time—been "fully informed" about the evidence that ondansetron was teratogenic in animals, evidence that would have supported, indeed presumably required, that Zofran be placed in Pregnancy Category C under the pre-2015 pregnancy labeling regulations. That is the warning that Plaintiffs contend was required under state law.

Under *Albrecht*, however, "fully informing" FDA of the justifications for a stronger warning is only half the test for preemption. The defendant manufacturer must also show that, after being fully informed, "the FDA . . . *informed* the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." 139 S. Ct. at 1678 (emphasis added). *That simply did not happen here*. Although GSK asked the agency to opine on the Japanese animal studies in its Citizen Petition, FDA declined to do so. And Novartis in its 2020 PAS application did not ask FDA to consider the Japanese animal studies; indeed, following GSK, it told FDA that those studies contained no evidence of teratogenicity and did not ask for any changes to the relevant sections of the label. FDA never commented on those studies in its ruling on Novartis's labeling application; indeed, there is no indication that FDA ever "considered" those studies at all.

The district court, nevertheless, ruled that FDA had "made the determination that a label change is not warranted." Addendum 6. It decided that it was "highly unlikely" that FDA would not have considered this thirty-year-old evidence—that Novartis had not asked the agency to consider and had told the agency contained "[n]o evidence of teratogenicity." Addendum 61. To conclude otherwise, the district court decided, would be "to assume that the FDA failed to perform, in fact blatantly ignored, its statutory duties to review and monitor the drug for human safety." *Id*. It therefore inferred clear evidence for preemption from FDA's silence. That decision

simply cannot be squared with the instructions of the Supreme Court in *Levine* and *Albrecht*, and must be reversed by this Court.

A. FDA Has Never Informed Either GSK or Novartis that It Would Not Permit a Change to Labeling to Indicate that the Japanese Animal Studies Revealed Evidence of Teratogenicity.

As a factual matter, it is undisputed that FDA never informed either GSK or Novartis that it would not permit a label change to reflect the fact that the withheld Japanese animal studies revealed evidence of teratogenicity.

As discussed above, GSK for the first time provided FDA with full reports of all eight Japanese animal studies in connection with its Citizen Petition filed in November 2019. PUB_007815. GSK asked the agency to "review the . . . information" and "either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling in light of . . . [this] information, as the Agency deems appropriate." PUB_007816. But FDA expressly declined to take a position on the information submitted by GSK. "[Y]our request that the Agency review limited categories of information and 'either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling' . . . is denied *without comment on the relevance, if any, of this information to ondansetron product labeling*." PUB_010469 (emphasis added). FDA explained:

> Your request that FDA review and opine on certain pieces of information to answer a hypothetical question separate and apart from FDA's ongoing product review would divert scientific staff time away

> from pending drug applications, drug product safety review, and other work critical to our public health mission and therefore would detract from fulfilling the Agency's statutory obligations. In addition, because a request to consider a hypothetical question is not a request to "take or refrain from taking" an administrative action, it is not the appropriate subject of a citizen petition (see 21 CFR § 10.25(a)).

Id.[18]

The only other regulatory action that has taken place since GSK provided the Japanese animal studies to FDA is the agency's consideration of Novartis's 2020 PAS application. But, here again, this regulatory action did not involve any FDA consideration of or comment on the Japanese animal studies. As discussed at greater length above, *supra* pp. 21–23, in June 2020 Novartis submitted a PAS proposing revisions to the pregnancy sections of Zofran's label [redacted]. UR_001661. Novartis, however, "did not propose any changes to the label's pregnancy risk summary

[18] FDA further explained:

> Given that FDA has limited resources to conduct its scientific evaluations in each of many substantive medical areas presented by drug applications, responding to this Petition would detract from and burden the current review of pending drug applications and drug product safety. Diverting staff time away from pending drug applications and drug product safety review to answer theoretical questions related to third-party litigation would detract from fulfilling the Agency's statutory obligations and public health mission.

PUB_010482.

section concerning animal studies or its animal data subpart within the pregnancy section." Addendum 23. Indeed, Novartis told FDA that it had reviewed all "[p]re-clinical data concerning reproductive toxicity associated with the use of ondansetron in pregnancy," *id.*, including the Japanese animal studies, Addendum 24, and had concluded that there was "[n]o evidence of teratogenicity based on preclinical studies," *id.*

Unsurprisingly, therefore, in responding to Novartis's application, FDA neither commented on any of the pre-clinical animal study data, nor did the Agency "propose any changes to the label's pregnancy 'Risk Summary' section concerning animal studies or its animal studies subpart within the pregnancy section." Addendum 26. Of course, FDA did not opine on the appropriateness of Zofran's former Pregnancy Category B labeling—since the pregnancy categories had been repealed six years earlier—but neither did the agency say anything about the appropriate treatment of the animal study data under the new pregnancy labeling rules.[19]

[19] As the district court noted, in FDA's final approval of Novartis's PAS after several rounds of revisions, FDA did "add[] the word 'oral' to one sentence in the pregnancy animal data subsection [for the injectable formulation] to identify how rats in a particular study received Zofran doses." Addendum 28. In context, it is clear that this change was intended to conform the labeling for injectable Zofran to the approved labeling for the other formulations of the drug, PUB_011019, and does not in any respect reflect an FDA reevaluation of the pre-clinical data.

Thus, at no time since FDA has been "fully informed" about the Japanese animal studies has the agency ever, "in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include [the] warning [Plaintiffs contend was required by state law]." *Albrecht*, 139 S. Ct. at 1678.

B. FDA Silence Cannot Constitute a Rejection of a Labeling Change, Especially in Light of the Change in the Regulatory Standards.

The district court nevertheless ruled that FDA had, *sub silentio*, "made the determination that a label change is not warranted." Addendum 6. That ruling was inconsistent with (1) the test established by the Supreme Court in *Albrecht*, (2) with the guidance in that case that only formal agency actions taken pursuant to congressionally delegated authority can have preemptive effect, and (3) with the general principle first announced in *Levine* that it is the drug manufacturer who bears primary responsibility for the adequacy of its labeling at all times. For each of these reasons, the district court's ruling must be reversed.

1. The District Court Ruling Violates *Albrecht*'s Requirement of Express FDA Disapproval.

Contrary to the district court's conclusion, there is simply no way to read FDA's responses to Novartis's 2020 PAS application as "inform[ing] the drug manufacturer that the FDA would not approve changing the drug's label," *Albrecht*, 139 S. Ct. at 1678, to include information about birth defects in animals whose mothers had been treated with Zofran in the Japanese animal studies, the warning

Plaintiffs contend was required by state law. Novartis did not ask FDA to consider those studies (indeed going so far as to inform the agency that, in the company's view, they did *not* reveal evidence of teratogenic effect), and each of FDA's responses to Novartis says nothing whatsoever about the Japanese studies. This cannot be the agency *informing* the manufacturer of its disapproval, as *Albrecht* requires.[20]

[20] By contrast, what FDA did do with the inconsistent human epidemiological data supports the notion that the agency would have permitted Novartis to add information about birth defects in the Japanese studies to the labeling. FDA permitted Novartis to include data from multiple human epidemiological studies in the "Human Data" section of the label, including studies that had found that ondansetron "was specifically associated with cardiac septal defects" and that "showed an increased risk of oral clefts" when "ondansetron was prescribed in the first trimester." PUB_011030–31. The agency permitted the inclusion of this data in the label, even though, as the label also states, "[a]vailable data on ondansetron use in pregnant women from several published epidemiological studies preclude an assessment of a drug-associated risk of adverse fetal outcomes due to important methodological limitations . . . ." PUB_011030.

This is directly comparable to what a former Pregnancy Category C label would have indicated. It would have noted that pre-clinical animal studies had revealed adverse effects on the fetus (as the Japanese animal studies do), and that there were no well-controlled studies in pregnant women. Therefore, the label would have stated that Pregnancy Category C drugs should only be prescribed where the prescribing physician believes the potential benefit justifies the potential risk to the fetus. Category C labeling would not have prohibited or categorically warned against use of Zofran during pregnancy. It would merely have alerted doctors and patients that there was some evidence from animal studies that should make them wary and that the drug should only be used where the likely benefits outweighed the potential risks. The current Zofran label, approved by FDA, similarly informs doctors and patients of human epidemiological studies finding associations between Zofran use and birth defects, while noting limitations on those studies and declining to warn against all use during pregnancy.

Albrecht's express disapproval requirement serves multiple important purposes. First, it provides clarity about FDA's position, the clarity required for "clear evidence" preemption of state law under *Levine*. *Cf. Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982) (noting preemption is only appropriate when the relevant federal and state laws "irreconcilably conflict": "The existence of a hypothetical or potential conflict is insufficient to warrant . . . pre-emption."). Second, it meshes nicely with *Albrecht*'s requirement that preemption can only arise from "formal agency action" under its congressionally delegated authority. How is one to determine that FDA has "formally" rejected a label change in the exercise of its statutory authority when its actions are silent as to that potential change? Third, and finally, *Albrecht*'s express disapproval requirement furthers the principle established in *Levine* that, "absent clear evidence" that FDA would not permit a label change, the manufacturer bears responsibility to ensure the adequacy of its labeling.

GSK cannot show that FDA, once in possession of all relevant scientific information, ever expressly informed either GSK or Novartis that it would not permit a labeling change to reflect the evidence of teratogenicity revealed in the Japanese animal studies. That, in and of itself, should be sufficient to defeat preemption.

2. The District Court Ruling Violates *Albrecht*'s Requirement of Formal Agency Action Pursuant to Congressional Authority.

The district court's ruling also violates the *Albrecht* requirement that only formal agency action pursuant to its statutorily delegated authority can lead to preemption. As the *Albrecht* majority explained:

> [T]he only agency actions that can determine the answer to the pre-emption question, of course are agency actions taken pursuant to the FDA's congressionally delegated authority. . . . Federal law permits the FDA to communicate its disapproval of a warning by means of notice-and-comment rulemaking setting forth labeling standards, by formally rejecting a warning label that would have been adequate under state law, or with other agency action carrying the force of law. . . . [W]hatever the means the FDA uses to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated.

139 S. Ct. at 1679 (internal citations omitted). Justice Thomas's concurring opinion also stressed this point:

> By its reference to "the Laws of the United States," the Supremacy Clause "requires that pre-emptive effect be given only to those federal standards and policies that are set forth in, or necessarily follow from, the statutory text that was produced through the constitutionally required bicameral and presentment procedures." Merck's primary argument, based on various agency communications, is that the FDA would have rejected a hypothetical labeling change submitted via the CBE process. But neither agency musings nor hypothetical future rejections constitute pre-emptive "Laws" under the Supremacy Clause.

Id. at 1682 (Thomas, J., concurring) (internal citation omitted). Justice Thomas concluded: "Because Merck points to no statute, regulation, or other agency action with the force of law that would have prohibited it from complying with its alleged

state-law duties, its pre-emption defense should fail as a matter of law." *Id.* at 1683–84.[21]

Of course, FDA's eventual 2021 approval of Novartis's revised label pursuant to its PAS application is formal agency action with the force of law. But that agency action says nothing about the Japanese animal studies. Novartis did not ask FDA whether it could include the results of those studies in its labeling and FDA did not tell the company that it was prohibited from doing so. The most that GSK, and the district court, could do was to infer that FDA would not have permitted Novartis to add the Japanese animal studies to the label *if* Novartis had asked for permission to do so. But that is not enough to warrant impossibility preemption under *Albrecht.* To quote Justice Thomas again:

> Merck's belief that the FDA would have eventually rejected a CBE application does not make an earlier CBE change impossible. As the Court correctly explains, "'the possibility of impossibility [is] not enough.'" The very point of the CBE process is that a manufacturer can

[21] *See also Lipschultz v. Charter Advanced Servs. (MN), LLC*, 140 S. Ct. 6 (Mem.), 2019 WL 5300908, at *7-8 (Oct. 21, 2019) (Thomas and Gorsuch, JJ., concurring in denial of cert.) ("It is doubtful whether a federal policy—let alone a policy of nonregulation—is 'Law' for purposes of the Supremacy Clause. Under our precedent, such a policy likely is not final agency action. . . . Giving pre-emptive effect to a federal agency policy of nonregulation thus expands the power of both the Executive and the Judiciary. It authorizes the Executive to make 'Law' by declining to act, and it authorizes the courts to conduct 'a freewheeling judicial inquiry' into the facts of federal nonregulation.").

> "unilaterally" make a labeling change that does not violate other federal law, at least until the FDA rules on its application.

Id. at 1683 (Thomas, J., concurring) (alteration in original) (internal citations omitted).

Because Novartis never asked FDA for permission to add information from the Japanese animal studies to the Zofran label, FDA has taken no formal agency action that would prohibit Novartis from unilaterally adding that information through the CBE process.[22] There is thus still no "irreconcilable conflict" between federal and state law, so the district court's ruling finding preemption was in error and must be reversed.

3. The District Court Ruling Violates *Levine*'s Principle that the Drug Manufacturer Bears Primary Responsibility for the Adequacy of Its Labeling.

Finally, the district court's ruling violates the core principle of the Supreme Court decision in *Levine* that it is the drug manufacturer, not FDA, that "bears responsibility for the content of its label at all times." 555 U.S. at 570-71.

[22] GSK, of course, did ask FDA to rule on that issue in its Citizen Petition, but FDA "denied [that petition] without comment on the relevance, if any, of this information to ondansetron product labeling," PUB_010469, deeming GSK's "request to consider a hypothetical question . . . not [to be] the appropriate subject of a citizen petition." PUB_010469.

The district court was simply unwilling to consider the possibility that FDA had only reviewed the evidence, and ruled on the labeling changes, that Novartis had asked the agency to consider:

> Accepting plaintiffs' argument would suggest that the FDA conducted a narrow and myopic review of the safety of the drug, considering only what Novartis expressly asked it to consider, and that it turned a blind eye to evidence that Zofran causes birth defects. That is highly unlikely, to say the least. . . . [T]hat assumes that the FDA was not following the statutory requirement that it consider "all" relevant information in evaluating the PAS. In this context, at least, the Court will not assume that the FDA failed to perform, in fact blatantly ignored, its statutory duties to review and monitor the drug for human safety.

Addendum 61.

Whether the district court's assumptions make any sense in the context of thirty-year-old animal data is almost beside the point. The Supreme Court has already rejected the district court's reasoning far more comprehensively: "The FDA has limited resources to monitor the 11,000 drugs on the market,[23] and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Levine*, 555 U.S. at 578-79 (footnote call number omitted). It is precisely for this reason that FDA has "traditionally regarded state law as a complementary form of drug regulation":

> State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured

[23] While there may have only been 11,000 approved drugs on the market at the time *Levine* was decided, there are now more than 20,000. PUB_012151.

> persons to come forward with information. Failure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times. Thus, the FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.

Id. at 579.[24]

As the Supreme Court has explained in both *Levine* and *Albrecht*, impossibility preemption is a "demanding defense." *Levine*, 555 U.S. at 573; *Albrecht*, 139 S. Ct. at 1678. GSK has not been able to show that it fully informed FDA about the Japanese animal studies—which revealed evidence of teratogenic effect—before 2019, nor that, after that date, FDA expressly prohibited a change to the Zofran labeling to reflect the results of those studies. The district court erred by assuming, based on nothing more than agency silence, that FDA had—or would have—rejected a CBE labeling change to alert prescribing doctors and patients to the results of the Japanese studies. Under both *Levine* and *Albrecht*, finding

[24] An echo of the Supreme Court's reasoning can be heard in FDA's statement included in its rejection of GSK's Citizen Petition:

> Your request that FDA review and opine on certain pieces of information to answer a hypothetical question separate and apart from FDA's ongoing product review would divert scientific staff time away from pending drug applications, drug product safety review, and other work critical to our public health mission and therefore would detract from fulfilling the Agency's statutory obligations.

PUB_010469.

preemption based on that assumption was clear error, and the decision below must be reversed.

CONCLUSION

For the foregoing reasons, the decision of the district court granting summary judgment based on preemption should be reversed, and the cause remanded for further proceedings.

March 16, 2022

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This document complies with the type-volume limit in this Court's Order of February 4, 2022, which granted Plaintiffs-Appellants request to file a brief not to exceed 15,000 words because, excluding the parts of the document exempted by the Fed. R. App. P. 32(f), this document contains 14,670 words.

This document complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6) because this document has been prepared in a proportionally spaced typeface using Microsoft Word in size 14 Times New Roman font.

March 16, 2022

/s Louis M. Bograd
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CERTIFICATE OF SERVICE

I hereby certify that on March 16, 2022 I electronically filed the foregoing with the Clerk of Court using the Court's CM/ECF system which will send notification of such filing to all counsel of record. I also certify that an unredacted copy of the foregoing will be sent by mail to the Clerk of Court and by e-mail to Counsel for Appellee.

/s Louis M. Bograd
Louis M. Bograd

Attorney for Plaintiffs-Appellants

ADDENDUM

ADDENDUM TABLE OF CONTENTS

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION	**MDL No. 1:15-md-2657-FDS**
This Document Relates To:	
All Actions	

MEMORANDUM AND ORDER ON DEFENDANT'S RENEWED MOTION FOR SUMMARY JUDGMENT BASED ON FEDERAL PREEMPTION

SAYLOR, C.J.

This is a multi-district litigation ("MDL") proceeding arising out of product-liability claims that the use of the drug Zofran (ondansetron) by pregnant women caused birth defects in their children. Defendant GlaxoSmithKline LLC ("GSK") has filed a renewed motion for summary judgment based on federal preemption—in substance, that state-law claims of failure to provide an adequate warning label are preempted by federal law.[1] For the following reasons, the motion will be granted.

I. Introduction

Zofran is an anti-emetic—that is, a drug that prevents or treats nausea or vomiting. It was initially approved by the Food and Drug Administration in 1991 for the prevention of nausea and vomiting induced by chemotherapy or radiation therapy and post-operative nausea and vomiting.

Zofran was not approved, and never has been approved, for the prevention of nausea and

[1] This Court originally denied a similar motion on February 5, 2019, on the ground that the issue of preemption presented disputed issues of material fact that precluded summary judgment. *See generally In re Zofran (Ondansetron) Prods. Liab. Litig.*, 368 F. Supp. 3d 94 (D. Mass. 2019). After that decision, the Supreme Court held in *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019), that preemption presented issues of law to be resolved by the judge, not a jury. GSK then renewed its motion on a supplemented factual record.

vomiting in pregnancy. Nonetheless, Zofran has been prescribed off-label to pregnant women for many years. According to plaintiffs, that widespread practice was due in large part to unlawful marketing practices by GSK that sought to promote off-label usage.

Plaintiffs in this case are principally women who took Zofran during pregnancy and their children, who are alleged to have a variety of birth defects, largely consisting of orofacial defects and cardiac ventricular and/or septal defects. The basic premise of each lawsuit is that Zofran caused those injuries, and that GSK failed to provide an adequate warning label concerning the risks of ingesting Zofran during pregnancy.

At some point, the FDA became aware that Zofran was being prescribed to pregnant women in significant numbers. In 2010, the FDA requested that GSK provide supplemental information concerning the safety of Zofran when used during pregnancy. In response, GSK provided an analysis of the then-available safety data. The FDA did not require any labeling changes. In 2013, a citizen petition requested that the FDA revise the Zofran label to indicate an increased risk to fetal safety if ingested during pregnancy. The FDA rejected that request. In 2015, the current manufacturer of Zofran, Novartis, submitted a proposed label change to the FDA to provide, among other things, a warning that use in pregnancy could cause harm to the fetus and is not recommended. That, too, was rejected. In 2019, GSK itself filed a citizen petition, asking that the FDA review various pieces of information concerning the safety of Zofran that plaintiffs allege had not been provided to the agency. In the course of that proceeding, counsel for both GSK and plaintiffs met with the FDA and provided information concerning the safety of Zofran. Although the FDA rejected the GSK petition, it did not require a label change.

Finally, in 2020, Novartis again submitted to the FDA a proposed label change with a

pregnancy warning, based largely on recently published epidemiological studies with new data. By that point, the FDA had been provided with every study and piece of scientific literature on which plaintiffs rely in this case to establish that Zofran causes birth defects. In early 2021, the FDA again rejected the proposed pregnancy warning.

Thus, the question of whether Zofran poses a sufficiently significant risk to fetal safety to justify an enhanced warning has been considered, and rejected, by the FDA on multiple occasions since the drug's initial approval. As of today, it is not contraindicated for use during pregnancy, and its label contains no enhanced form of warning for such use. Indeed, the current label states that "[p]ublished epidemiological studies on the association between ondansetron use and major birth defects have reported inconsistent findings and have important methodological limitations that preclude conclusions about the safety of ondansetron use in pregnancy."

Plaintiffs nonetheless contend that ingestion of Zofran during pregnancy in fact causes birth defects, that the label should contain a warning to that effect, and that GSK's failure to provide such a warning should result in tort liability under state law. Plaintiffs further contend that the FDA's initial approval of Zofran in 1991, and its subsequent rejections of label changes, were based on incomplete information—essentially, because GSK withheld certain data from the FDA and made material misrepresentations—and that the FDA did not specifically address certain animal studies that plaintiffs say show a risk of fetal injury. Plaintiffs thus argue that their state-law claims are not preempted by federal law.

The preemption issue arises out of a clash between federal regulation of prescription drugs and state-law product-liability principles. By federal law, the FDA closely regulates the labeling of drugs, including warning labels; as a general matter, a drug label may only be created or changed with FDA approval. That creates an obvious tension with state laws, which generally

permit recovery for failure to provide an adequate warning, but which assume that a manufacturer is free to provide such warnings as it sees fit.

The process of considering labels, and label changes, at the FDA is relatively complex. Among other things, the FDA does not simply "approve" or "reject" labels. It requires the submission of medical and scientific data and analysis with a proposed label. And it mandates the form and layout of the label and scrutinizes its content, down to the most minute details, in what is typically an interactive process with the pharmaceutical company. It may reject or approve a particular form of wording, or mandate certain changes.

Furthermore, the FDA's approach to warning labels is very different from the manner in which state-law tort principles drive the labeling of consumer products as a general matter. The FDA is concerned not only with avoiding insufficient warnings (that is, failing to warn against risks), but also avoiding over-warning (that is, warning against risks that are unduly speculative, hypothetical, or not adequately supported by science). Thus, while a consumer product such as a chainsaw might bear dozens and dozens of warnings, with little regard for the remoteness or obviousness of the risk, the FDA takes a more measured approach that is intended to provide accurate information to medical professionals and patients without unduly discouraging the use of the product.

Normally, therefore, an FDA-approved warning is mandatory, and does not represent a minimum, or a "floor," that the pharmaceutical company may exceed in its discretion. There is, however, a process under federal law—called the "changes being effected," or "CBE," process—that permits a drug company to change a label unilaterally, based on certain "newly acquired information" concerning a drug's safety, subject to later FDA approval. Because of the existence of the CBE process, the Supreme Court has held that a pharmaceutical company can in fact add

safety information to its label without FDA approval, at least in the short term. *See Wyeth v. Levine*, 555 U.S. 555, 570-71 (2009). In addition, a pharmaceutical company can seek a label change by filing a "Prior Approval Supplement" ("PAS") requesting revisions to the label, which the FDA must approve before implementation. That, in fact, is what Novartis did in 2020. And anyone, even a private individual, can request a label change through a citizen petition submitted to the FDA. Finally, the FDA has an independent duty imposed by statute to require label changes if it becomes aware of new information that it determines should be included in the drug's label.

The interaction between the FDA process and state tort law has created a variety of difficult legal questions over the years. Indeed, the Supreme Court has considered the preemption issue three times over the past dozen or so years without resolving all of the significant questions. *See Wyeth*, 555 U.S. 555 (2009); *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011); *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019). In *PLIVA*, the court found that state-law claims are preempted when a manufacturer could not use the CBE process and unilaterally change the label. 564 U.S. at 623-24. In *Albrecht*, the court framed the preemption inquiry—assuming a manufacturer could avail itself of the CBE process—as having two parts: the manufacturer must show first "that it fully informed the FDA of the justifications for the warning required by state law," and second, "that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." 139 S. Ct. at 1678.

Here, the Court will assume, without deciding, that GSK had the ability to change the Zofran label unilaterally through the CBE process prior to the time it sold the rights to the drug to Novartis in 2015. For the reasons set forth below, the Court concludes that the FDA has been

fully informed of the justifications for the warning proposed by plaintiffs—in particular, the scientific studies and literature, including the disputed animal studies, concerning the likelihood that Zofran poses a risk to the fetus when ingested by pregnant women. There is no basis at this point for concluding that any relevant information had been withheld from the FDA by the time of its 2021 decision. The Court further concludes that there is no doubt that the FDA would *not* approve the changes to the warning label proposed by plaintiffs. It has effectively rejected those changes, and indeed approved contrary language.

One potential wrinkle in the analysis arises from the fact that GSK submitted the original new drug applications for Zofran to the FDA, beginning in 1991, but then sold the rights to the drug to Novartis in 2015. Subsequently, Novartis proposed changes to the label through the PAS process on two different occasions, both of which the FDA rejected. The FDA therefore informed Novartis—not GSK—that it would not approve the proposed changes. And there was never a point between 1991 and 2015 when the FDA prevented GSK from changing the label. Nonetheless, for the reasons set forth below, there is no reasonable basis to treat GSK and Novartis differently for purposes of the preemption analysis.

In short, even assuming that GSK did, in fact, fail to make complete disclosures to the FDA in 1991, and at various later points, there is no question that the FDA is now fully informed of all relevant information concerning the safety of the drug. And the FDA has made the determination that a label change is not warranted. Thus, the FDA, acting pursuant to the duty imposed on it by federal law, has rejected the pregnancy warning label that plaintiffs insist was required by state law at the time of the alleged injuries.

Accordingly, and for the following reasons, plaintiffs' state-law claims of failure to warn are preempted by federal law, and GSK's renewed motion for summary judgment based on

federal preemption will be granted.

II. Background

Unless otherwise noted, the following facts are undisputed.

A. The Regulatory Framework

1. Labeling Requirements Generally

Under federal law, a drug company may not market or sell a new pharmaceutical drug without the approval of the Food and Drug Administration. 21 U.S.C. § 355(a). To obtain that approval, the company (which is referred to as the "sponsor") must submit a New Drug Application ("NDA") to the FDA. *Id.* An NDA must provide comprehensive information about the drug, including its formulation, the proposed labeling, and scientific data about its safety and efficacy. *Id.* §§ 355(b)(1)(A)(i), (iii), (vi); 21 C.F.R. §§ 314.50(d)(5)(viii), 201.57(a).

Not surprisingly, FDA regulations require that an NDA fully disclose all "pertinent" safety information. *See, e.g.*, 21 C.F.R. §§ 314.50 (requiring "reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source"); 314.50(d)(5)(vi)(a) (requiring "an integrated summary of all available information about the safety of the drug product, including pertinent animal data[and] demonstrated or potential adverse effects of the drug"); 312.50 (stating that "[s]ponsors are responsible for . . . providing [investigators] with the information they need to conduct an investigation properly . . . and ensuring that [the] FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug").

The sponsor's duty to make full disclosure continues beyond the initial submission of its NDA. *See, e.g.*, *id.* §§ 314.50(d)(5)(vi)(b) ("The applicant must . . . update periodically its pending NDA with new safety information learned about the drug that may reasonably affect the

statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling . . . [including information from] animal studies . . . ."); 312.33 (requiring annual reports for investigational NDAs that include "[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," and, "[i]f the study has been completed, or if interim results are known, a brief description of any available study results").

The FDA approval process is "onerous and lengthy." *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013). The FDA will approve a drug only if the NDA demonstrates that the drug (1) is "safe for use," (2) "will have the effect it purports or is represented to have," and (3) is accompanied by labeling that is neither "false [n]or misleading in any particular." 21 U.S.C. §§ 355(c)(1)(A), (d).

The FDA does not only approve the drug and its intended use; it also approves the exact text of the label. *Id.* § 355; *see Wyeth*, 555 U.S. at 568. With one exception, noted below, the sponsor may not alter the label in any respect without the approval of the FDA. *Wyeth*, 555 U.S. at 568.

2. <u>The Process for Changing Labels</u>

After approval of a drug, the FDA retains the authority to require changes to the label to reflect new information concerning its safety and efficacy. 21 U.S.C. § 355(o)(4) ("If the Secretary becomes aware of new information, including any new safety information . . ., that the Secretary determines should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person . . . ."). Nonetheless, a "central premise of federal drug regulation [is] that the manufacturer bears responsibility for the content of its label at all times." *Wyeth*, 555 U.S. at 570-71. The manufacturer is "charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* at 571.

There are two ways in which a manufacturer can seek to change the warnings on a drug label. *See In re Celexa & Lexapro Mktg. & Sales Pracs. Litig.*, 779 F.3d 34, 37 (1st Cir. 2015) (citing 21 C.F.R. §§ 314.70(b)(2), (c)(6)).

First, a manufacturer can file a "Prior Approval Supplement" ("PAS") requesting revisions to the label. 21 C.F.R. § 314.70(b). That process requires FDA approval before implementation, and in substance is similar to the process for initial approval of a label.

Second, a manufacturer can unilaterally amend a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" when "newly acquired information" reflects a "clinically significant hazard." 21 C.F.R. §§ 201.57(c)(6)(i), 314.70(c)(6)(iii). That action, known as the "changes being effected" ("CBE") process, allows a sponsor to make an immediate labeling change upon filing a supplemental application with the FDA. The amended label will then be reviewed by the FDA and will be approved if it is based on new "reasonable evidence of a causal association with [the] drug" and a "clinically significant hazard." 21 C.F.R. § 201.57(c)(6)(i).

The term "newly acquired information" is not limited to entirely new data. *Wyeth*, 555 U.S. at 569. It also includes the following:

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

21 C.F.R. § 314.3; *see also Celexa*, 779 F.3d at 42 (giving examples of "newly acquired information").

3. The FDA's Approach to Warning Labels

For most types of consumer products, manufacturers have an incentive to warn against

every conceivable type of hazard or risk in order to try to forestall tort liability under state law. Many products thus come covered with labels, and packaged with booklets, containing multiple warnings against dangers both real and remote.

> With pharmaceuticals, however, the FDA has adopted a more balanced approach.
>
> [T]he FDA does not simply approve warnings out of an abundance of caution whenever the manufacturer posits a theoretical association between drug use and an adverse event. As the FDA has recognized, "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug." Moreover, "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance." Accordingly, the FDA will reject a PAS application or CBE amendment if there is insufficient evidence of a causal link between drug use and the adverse event.

In re Fosamax (Alendronate Sodium) Prods. Liab. Litig., 852 F.3d 268, 274 (3d Cir. 2017) (citations omitted).

The FDA standard for requiring a warning label is thus different from that imposed by state tort law. *See, e.g.*, *PLIVA*, 564 U.S. at 611 ("It is undisputed that Minnesota and Louisiana tort law require a drug manufacturer that is or should be aware of its product's danger to label that product in a way that renders it reasonably safe."); *Wooderson v. Ortho Pharm. Corp.*, 681 P.2d 1038, 1049 (Kan. 1984) ("It is well settled, however, that the manufacturer of ethical drugs bears the additional duty of making timely and adequate warnings to the medical profession of any dangerous side effects produced by its drugs of which it knows, or has reason to know.") (collecting cases from various jurisdictions).

4. Warning Labels for Pregnancy

Special provisions govern the labeling of drugs that may be taken by pregnant women. Until June 30, 2015, the FDA classified drugs into five categories of safety for use during pregnancy: A, B, C, D, or X. According to the then-applicable statutory language, "[i]f animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and

well-controlled studies in pregnant women," the label must contain the following language:

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

21 C.F.R. § 201.57(c)(9)(i)(A)(2).

Alternatively, "[i]f animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks," the label must contain the following language:

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

21 C.F.R. § 201.57(c)(9)(i)(A)(3).

That classification system was eliminated by the FDA when it issued a final rule amending the regulations concerning pregnancy and lactation labeling. Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, 79 Fed. Reg. 72,064 (Dec. 4, 2014).

B. <u>The Approval of the Zofran Label</u>

Zofran, or ondansetron hydrochloride, is a prescription drug that prevents nausea and vomiting. It is part of a class of anti-emetics referred to as selective serotonin 5-HT3 receptor antagonists. (Hill Decl., Ex. 75).

On January 4, 1991, the FDA approved the marketing and sale of Zofran for the prevention of nausea and vomiting induced by chemotherapy or radiation therapy and post-

operative nausea and vomiting. (*Id.*, Ex. 19).[2] The 1991 approval was for an injection formulation; in 1992, 1995, 1997, and 1999, the FDA approved four additional formulations, covering oral tablets, premixed injections, oral solutions, and orally disintegrating tablets, respectively. (*Id.*, Exs. 19, 22-25).

C. The Use of Zofran by Pregnant Women

Nausea and vomiting during pregnancy ("NVP") is a common condition affecting 50% to 90% of women during their pregnancies. (*Id.*, Ex. 32 at 3). The most severe form of NVP is known as hyperemesis gravidarum ("HG"). (*Id.*). "HG has been reported in 0.5% to 2% of pregnancies and is characterized by persistent and severe nausea and vomiting," and may pose a serious health risk to both the mother and the fetus. (*Id.*).

Zofran was *not* approved by the FDA for treatment of nausea and vomiting during pregnancy. Indeed, GSK never sought approval for that use. However, it is generally lawful for physicians to prescribe medications for purposes for which they have not been FDA-approved (although it is generally unlawful for pharmaceutical companies to promote such "off-label" use). *See United States ex rel. Carpenter v. Abbott Lab'ys, Inc.*, 723 F. Supp. 2d 395, 397 n.2, 398-99 (D. Mass. 2010); *see also Buckman Co. v Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001) (noting that "'off-label' usage of medical devices . . . is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine"). Over time, many physicians have prescribed Zofran to pregnant women, particularly those suffering from HG.

When the FDA approved Zofran in 1991, it classified it as a pregnancy category B drug.

[2] A predecessor of GSK, Glaxo, Inc., sponsored the original new drug application for Zofran. (Master Compl. ¶ 4).

(Hill Decl., Ex. 19 at 8). Between 1992 and 2016, the "Use in Specific Populations" section of the approved label for intravenous Zofran containing the pregnancy category B designation contained the following or similar language:

> Reproduction studies have been performed in pregnant rats and rabbits . . . 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.

(*Id.*, Ex 20; *see also* Exs. 32, 40).

The Zofran label does not, and never has, contained a warning contraindicating use of the drug to treat pregnant women.

D. The 2010 FDA PAS Request

In December 2010, then-FDA Director Donna Greibel sent GSK a "Prior Approval Supplement Request" concerning Zofran. The PAS Request indicated that the FDA was aware of the common use of Zofran during pregnancy and requested that GSK "review and analyze available published and unpublished literature on the use of ondansetron during pregnancy and lactation, with a focus on the presence or absence of adverse pregnancy and/or neonatal outcomes." (*Id.*, Ex. 26). The requested review and analysis was to include an "assessment of the strengths and limitations of the data" and proposed labeling revisions if GSK concluded changes were necessary to "furnish adequate information for the safe use of this drug." (*Id.*).

In April 2011, GSK replied to the FDA. Its response stated that it had "completed a review of the available data and ha[d] included a summary of that analysis in [its] submission." (*Id.*, Ex. 27). It stated that "[its] position is that the use of [Zofran] in human pregnancy has not been established and is not recommended." (*Id.*). And it concluded that it "[did] not believe there [was] sufficient evidence to warrant a change in the [Zofran label]." (*Id.*).

The FDA did not respond and no changes were made to the Zofran label concerning pregnancy. (*Id.*, Ex. 28).

E. The 2013 Reichmann Citizen Petition

In January 2013, an individual named James P. Reichmann submitted a citizen petition asking the FDA to revise the Zofran label to provide heightened pregnancy warnings. (*Id.*, Ex. 29).[3] Specifically, he requested that the FDA reclassify the drug's pregnancy risk category from B to C, D, or X; notify obstetricians and gynecologists "that there is insufficient scientifically acceptable evidence that ondansetron is associated with improved treatment outcomes and may lead to adverse maternal and fetal events or outcomes"; and notify obstetricians and gynecologists that "promotion of continuous subcutaneous ondansetron pump for the treatment of nausea and vomiting of pregnancy (NVP) is a violation of FDA regulations." (*Id.*, Ex. 32 at 1). His petition contended that Zofran "may lead to adverse maternal and fetal events or outcomes" if ingested during pregnancy. (*Id.*).[4]

On October 27, 2015, the FDA denied the petition. (*Id.* at 2). The FDA noted that ondansetron had not been approved for the treatment of NVP, but that it was "aware of the unapproved use of oral and injectable ondansetron for the treatment of NVP." (*Id.* at 3). It stated that "[t]he available evidence is not sufficient to conclude that there is an increased risk of birth defects, including cleft palate, among fetuses exposed to ondansetron." (*Id.* at 13). It further indicated that it considered "information submitted by [GSK] to support approval of the

[3] A citizen petition is a request that the 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). A citizen may petition for a change in drug labeling. *See Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1102 (10th Cir. 2017) (noting that "the FDA standard for revising a warning label does not discriminate between proposals submitted by manufacturers and proposals submitted by citizens").

[4] Reichmann supplemented his petition five times. (Hill Decl., Ex. 32 at 1).

ondansetron NDA," "post-marketing drug and device adverse event data," and scientific literature obtained through public submissions and through its own "targeted searches." (*Id.* at 18 n.56). It concluded:

> Taking into consideration both the data available at the time ondansetron was approved and subsequent human data gathered in the post approval setting, at this time the totality of the data do not support a conclusion that there is an increased risk of fetal adverse outcomes, including birth defects such as cleft palate and cardiac ventricular and/or septal defects, among fetuses exposed to ondansetron.

(*Id.* at 18).

As to the warning label, the FDA stated: "[W]e believe pregnancy category B was the appropriate risk category for ondansetron when it was assigned and . . . we believe pregnancy category B remains appropriate today." (*Id.*). The FDA similarly rejected Reichmann's request for the FDA to notify doctors that use of Zofran during pregnancy is not safe for the fetus. (*Id.* at 19). Such a notification, the FDA explained, could actually be misleading on account of the fact that "the available data do not support a conclusion that there are increased safety risks . . . for the fetus." (*Id.* at 19).

F. The 2015 Novartis Proposal

Novartis acquired the rights to Zofran from GSK in 2015. On September 22, 2015, Novartis submitted to the FDA a proposed update to the Zofran pregnancy labeling along with a clinical overview. (*Id.*, Ex. 33).[5] The proposal included several changes to the pregnancy "Risk Summary" section of the label to advise against using Zofran during pregnancy and warn of potential risks to a developing fetus.

Specifically, Novartis proposed the following revisions:

- Beginning the "Risk Summary" subsection (§ 8.1) with the caution:

[5] Novartis was required to submit a proposed update to the Zofran label in order to conform with the then-new Pregnancy and Lactation Labelling Rule, published in December 2014. (Hill Decl., Ex. 33).

> "It is possible that ZOFRAN can cause harm to the fetus when administered to a pregnant woman. Thus, the use of ZOFRAN in pregnancy is not recommended. If ZOFRAN is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus." (*Id.* at 2090).

- In the "Risk Summary" section, including the statement "Animal studies are not always predictive of human response, therefore, the use of ondansetron in pregnancy is not recommended." (*Id.*).

- Creating a new subsection (§ 8.3) entitled "Females and males of reproductive potential," which discusses pregnancy testing and contraception and states, in part, "Advise females of reproductive potential that it is possible that ZOFRAN can cause harm to the developing fetus. (*Id.* at 2092).

Novartis also provided a 47-page "clinical overview" document summarizing the data that it believed was sufficient to support its revisions and a detailed recitation of the then-available adverse event data. (*Id.*, Ex. 34).

In the conclusion section of that document, Novartis stated that while a review of the science did not offer "consistent or compelling evidence that exposure to ondansetron in early pregnancy causes major birth defects, including congenital cardiac defects," the FDA should nevertheless accept its labeling changes that inform prescribers and patients "of the potential risk of fetal harm during treatment in pregnancy." (*Id.* at 2309).

In November 2015, the FDA rejected that request. It deleted the paragraph that included the sentence "[i]t is possible that ZOFRAN can cause harm to the fetus when administered to a pregnant woman." (*Id.*, Ex. 35 at 3945). It also deleted the subsection concerning "[f]emales and males of reproductive potential" in its entirety, stating that "the available human data do not support a clear conclusion on an increased risk of major congenital malformations," and therefore it did "not agree with recommendations for pregnancy testing and contraception use." (*Id.* at 3947).

In December 2015, Novartis submitted a new round of proposed changes to the pregnancy labeling. It cited reported adverse events as sufficient to warrant a statement that "[c]ases of congenital malformations have been reported in infants whose mothers took ondansetron during pregnancy." (*Id.*, Ex. 36 at 3902). And in an effort to "provide conservative guidance due to the potential off[-]label use and the data available," it again suggested including a warning that "[t]he safety of ondansetron for use in human pregnancy has not been established." (*Id.* at 3903). In light of reported off-label use, it also requested a new "Limitations of Use" section stating that "Zofran has not been studied in pregnant women for the prevention of nausea and vomiting." (*Id.* at 3896).

The FDA responded in April 2016, again rejecting proposed language that the "use of ondansetron in pregnancy is not recommended." (*Id.*, Ex. 37 at 4052; *see also id.*, Ex. 35 at 3945). The FDA stated that a "Limitations of Use" statement is "not intended to prohibit off-label use." (*Id.*, Ex. 37 at 4045). Rather, such a statement is proper only when "there is a known risk that outweighs the therapeutic benefits in a certain clinical situation," and the FDA could not draw that conclusion for the use of Zofran to treat NVP. (*Id.*).

Eventually, later in 2016, Novartis and the FDA agreed upon a revised label. In the communications leading up to the revision, the FDA made the following statements:

- "We do not agree with keeping [the phrase 'Animal studies are not always predictive of human response, therefore, the use of ondansetron in pregnancy is not recommended'] in labeling based on the available human information." (*Id.*, Ex. 35 at 3945).

- "Based on the Agency's review, the available human data do not support a clear conclusion on an increased risk of major congenital malformation." (*Id.* at 3947).

- "Based on review of the submitted pharmacovigilance database and the literature, we did not conclude that there is a basis to believe there is a causal relationship between the congenital malformations and the use of ondansetron. Therefore, these malformations would not qualify as adverse

reactions." (*Id.*, Ex. 37 at 4051).

- "[C]linical evidence do not demonstrate a consistent safety concern that warrants advising against use during pregnancy." (*Id.* at 4056).

- "There is no preponderance of evidence to show that Zofran is ineffective when used for nausea and vomiting in pregnancy . . . . There is also no preponderance of evidence that the benefits [of Zofran] do not generally outweigh its risks." (*Id.*, Ex. 39 at 4445).

- "[W]e do not believe that there is any basis to suspect drug attribution to [reported] congenital malformations cases for them to qualify as 'adverse reactions.' Only adverse reactions, where there is some basis to believe that the drug plays a role in the adverse outcome, should be included in labeling, including in the [Postmarketing] section." (*Id.* at 4450).

- "[T]here is no evidence, nonclinical or mechanism of action, that raises concerns for adverse fetal outcomes with Zofran. Inclusion of such statement would not only be unhelpful to prescribers, but it could be misleading in implying that FDA has some concerns about the role of Zofran in a variety of fetal malformations." (*Id.* at 4451).

- "[C]ardiac malformations is the most common congenital malformation, affecting nearly 1% of births per year in the US. Given such high prevalence, it is expected that such malformations would be reported with the use of Zofran by chance alone." (*Id.* at 4465).

The final 2016 version of the approved label stated the following, among other things:

- "Available data do not reliably inform the association of ZOFRAN and adverse fetal outcomes," (*id.*, Ex. 40 at 8);

- "Published epidemiological studies on the association between ondansetron and fetal outcomes have reported inconsistent findings and have important methodological limitations hindering interpretation," (*id.*);

- There is "no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate," (*id.* at 9); and

- There are "[i]mportant methodological limitations" to the single cohort study that reported an association between ondansetron exposure and cardiac defects, (*id.* at 8).

G. The 2019 GSK Citizen Petition

On November 1, 2019, GSK submitted a citizen petition asking the FDA to "review four

categories of information concerning the use of [Zofran] in pregnancy." (Hill Suppl. Decl., Ex. 160 at 1). Those categories are the four primary categories of evidence that plaintiffs allege GSK omitted in its Zofran submissions to the FDA: (1) results from three animal studies performed between 1988 and 1990 by a GSK affiliate in Japan; (2) data concerning the biological mechanism of action; (3) adverse event data; and (4) a 2004 birth defect study published by Adrienne Einarson *et al*. (*Id.* at 2). The petition stated:

> GSK requests that [the] FDA either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling in light of these four categories of information, as the Agency deems appropriate. If the Agency deems it appropriate to alter the labeling, GSK respectfully requests that the Agency inform GSK and the public which categories of information (if any) necessitated a labeling change, whether the Agency believes it did not already have the information, and/or why the information is material to the Agency's labeling decision.

(*Id.* at 1-2). GSK attached 59 exhibits to the petition. (*Id.*, Ex. 161). Included among those exhibits were (1) full study reports, including the supporting data, for the Japanese animal studies; (2) Dr. Bengt Danielsson's 2014 paper that described a biological mechanism of action for Zofran; (3) Dr. Danielsson's 2018 paper that discusses the Japanese animal studies and the mechanism of action theory; (4) the adverse event reports from GSK's Safety Database that plaintiffs allege GSK failed to properly report to the FDA; and (5) the *Einarson* study. (*Id.*).

The FDA opened an official agency proceeding upon receipt of the petition. (*Id.*, Ex. 198).

On January 8, 2020, plaintiffs filed a formal comment to the FDA requesting dismissal of the petition. (*Id.*, Ex. 184). On January 23, 2020, the FDA invited counsel for GSK and plaintiffs to each meet with the FDA to present their views on the petition. (*Id.*, Ex. 201).

On March 5, 2020, representatives from and counsel for GSK met with FDA representatives from the Office of the Chief Counsel and the Office of Regulatory Policy in the

FDA's Center for Drug Evaluation and Research ("CDER"), the entity responsible for regulating prescription drugs. (*Id.*, Ex. 202). At the meeting, GSK presented a PowerPoint presentation with information on each of the four categories of information the petition asks the FDA to consider. (*Id.*, Ex. 203). The FDA posted the minutes from the meeting and the PowerPoint presentation on the petition's public docket. (GSK Suppl. SMF ¶¶ 13-14).

On March 30, 2020, counsel for plaintiffs met with FDA representatives from the Office of the Chief Counsel and the Office of Regulatory Policy in CDER. (Hill Suppl. Decl., Ex. 204). At the meeting, plaintiffs presented a legal memorandum on federal preemption issues raised by the petition, a PowerPoint presentation with information on the four relevant categories of information, and a PowerPoint presentation on pregnancy labeling. (*Id.*, Exs. 205-07). The FDA posted the minutes from the meeting and the materials presented by plaintiffs to the petition's public docket. (GSK Suppl. SMF ¶¶ 24-25).

On April 13, 2020, plaintiffs submitted to the FDA an additional 30 attachments as an appendix to their presentation, including (1) Dr. Danielsson's expert report in this case from July 5, 2018; (2) Dr. Danielsson's rebuttal expert report in this case from August 27, 2018; (3) Dr. Brian Harvey's declaration and expert report in this case from September 26, 2018; (4) the deposition of Dr. Danielsson in this case from October 12, 2018; and (5) Dr. Danielsson's 2018 publication. (Hill Suppl. Decl., Ex. 208).

On January 15, 2021, the FDA denied the petition "without comment on the relevance, if any, of [the] information to ondansetron product labeling." (Notice by Plaintiffs' Lead Counsel of FDA Denial of GSK's Citizen Petition, January 15, 2021, Ex. A at 2).[6] In its decision, the

[6] It does not appear that plaintiffs submitted an affidavit authenticating Exhibit A. However, it is not in dispute that the exhibit in question is the FDA's response to GSK's citizen petition.

FDA provided a brief summary of Zofran's labeling history and described the current labeling concerning Zofran's use during pregnancy. (*Id.* at 13-14).[7] But it determined that GSK's request to consider a hypothetical question was not the "appropriate subject of a citizen petition." (*Id.* at 2 (citing 21 CFR § 10.25(a)). It further noted that the FDA "evaluates whether safety-related labeling changes are warranted based on the review of *all* relevant information available" to it. (Notice by Plaintiffs' Lead Counsel of FDA Denial of GSK's Citizen Petition, January 15, 2021, Ex. A at 2). Thus, it concluded that "any substantive conclusions" reached by the FDA in response to the petition "would not necessarily determine the information that should be communicated in the Zofran labeling today." (*Id.* at 15) ("For example, even if FDA were to determine that none of the four categories of information, in isolation, warranted a change to the Zofran labeling, that determination could change when considering the evidence in combination with other, more recent information . . . ."). It thus denied the petition "without comment on the relevance, if any, of [the four categories of] information to ondansetron product labeling." (*Id.* at 2).

Instead, the FDA "respond[ed]" to the petition "by providing background information on safety-related labeling for prescription drugs that may be helpful in clarifying FDA's expectations for application holders' submissions of postmarketing safety-related information and corresponding updates to product labeling and FDA's approach to the review of such information in the context of relevant statutory and regulatory requirements." (*Id.*). It intended for the response "to convey the depth of FDA's engagement in the scientific evaluation of relevant data and information in determining the safety-related information that should be

[7] The FDA cited a slide presented by GSK in its March 5, 2020 meeting in this discussion. (Notice by Plaintiffs' Lead Counsel of FDA Denial of GSK's Citizen Petition, January 15, 2021, Ex. A at 13 n.46).

included in FDA-approved labeling, and the iterative, bilateral nature of the communications process between FDA and the applicant or application holder regarding the content and wording of product labeling." (*Id.*). It concluded by stating that the FDA would "continue to monitor and review available safety information related to ondansetron products throughout the product life cycles" and would "take further action" if the FDA deem[ed] "it is appropriate to do so." (*Id.* at 16).

H. The 2020 Novartis Proposal

On June 4, 2020, Novartis submitted a new PAS to the FDA proposing revisions to the pregnancy section of Zofran's label and the inclusion of additional information concerning the use of Zofran in females and males of reproductive potential. (Hill Suppl. Decl., Exs. 189-90). It proposed those changes "based on recently published epidemiological studies with new data on the risk of birth defects." (*Id.*, Ex. 190 at 1).[8] It also noted in its clinical overview submitted to justify the changes that in advance of the submission a "cumulative search was conducted in the Novartis safety database," and included a discussion on the adverse event reports received up until the time of its submission. (*Id.*, Ex. 193 at 8, 20-25).

Specifically, Novartis proposed, in part, the following revisions:

- Beginning the "Risk Summary" pregnancy subsection (§ 8.1) with the caution:

  "In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy. Regarding cardiac malformations, the epidemiological studies showed conflicting results . . . . The use of ondansetron in pregnancy is not recommended." (*Id.*, Ex. 192 at 7534).

- Removing the statement that "[a]vailable data do not reliably inform the association of ZOFRAN and adverse fetal outcomes. Published epidemiological studies on the association between ondansetron and fetal outcomes have reported

[8] The studies were all published after February 2018. (Hill Suppl. Decl., Ex. 193 at 9).

inconsistent findings and have important methodological limitations hindering interpretation." (*Id.*).

- Creating a new subsection (§ 8.3) entitled "Females and Males of Reproductive Potential," which discusses pregnancy testing and contraception and states, in part, "Advise females of reproductive potential that it is possible that ZOFRAN can cause harm to the developing fetus." (*Id.* at 7535-36).

- Adding a subsection on "Pregnancy and Contraception" to the "Patient Counseling Information" section (§ 17), which states, "Advise female patients of reproductive potential: 1) It is possible that ZOFRAN can cause fetal harm; 2) inform their healthcare provider if they are pregnant or become pregnant; 3) use effective contraception during treatment and for 2 days after stopping treatment." (*Id.* at 7546).

Novartis proposed those revisions because it had "conducted a new analysis of recently published epidemiological studies that showed an increase in orofacial clefting in infant[s] of women exposed to ondansetron during the first trimester of pregnancy." (*Id.* at 7534). Thus, "[c]onsidering the overall risk of congenital defects and limited data on the effect of Zofran on the fetus when used during pregnancy," Novartis believed it was "important to recommend that patients not use Zofran during pregnancy." (*Id.*). In its clinical overview, however, Novartis noted that the "published epidemiological studies have various methodological limitations that preclude definitive conclusions about the safety of ondansetron," and that "[t]here is no evidence of association between ondansetron and the overall risk of birth defects." (*Id.*, Ex. 193 at 25).

Novartis did not propose any changes to the label's pregnancy risk summary section concerning animal studies or its animal data subpart within the pregnancy section. (*Id.*, Ex. 192 at 7534-35). The label states that "[r]eproductive studies in rats and rabbits did not show evidence of harm to the fetus" and that "there were no significant effects of ondansetron on the maternal animals or the development of the offspring." (*Id.*).

In its clinical overview, Novartis noted that before its submission it reviewed "[p]re-clinical data concerning reproductive toxicity associated with the use of ondansetron in

pregnancy." (*Id.*, Ex. 193 at 8). It concluded that those studies found that "ondansetron did not affect embryo-fetal development in the rat or rabbit and had no adverse effects on fertility or on the general reproductive performance and the post-natal development of rats." (*Id.* at 9). Thus, it concluded that there was "[n]o evidence of teratogenicity based on preclinical studies." (*Id.* at 25). In its specific discussion of that data, it commented on papers that discuss the Japanese animal studies (authored by Shimizu *et al.*) and the 2018 paper by Dr. Danielsson that discusses the proposed biological mechanism of action:

> Recent publication by Danielsson B et al (2018), aims to provide a mechanistic explanation of hERG block mediated teratogenicity in rat embryos in vitro based on alterations in embryonic heart rhythm. However, no embryo toxicity was observed in studies (oral or i.v.) performed by Shimizu M et al (1992) (oral), Shimizu M et al (1992) (i.v). There was also no effects on the post-implantation loss or the number of live fetuses. The teratogenicity of ondansetron referenced by Danielsson B et al (2018) from Shimizu M et al (1992) (oral) and Shimizu M et al (1992) (i.v) is questionable and does not provide clear evidence of a teratogenic potential. Furthermore, two additional rat studies submitted to FDA did not show any effects albeit they were performed at lower doses. However, the oral high dose group in oral route of 15 mg/kg/d should have some findings as Danielsson reported both 10 and 40 mg/kg/d as teratogenic based on Shimizu M et al (1992) (oral) oral study. In a book entitled "Catalog of teratogenic agents by Shepard TH, Lemire R (2004)," both the Shimizu M et al (1992) (oral), Shimizu M et al (1992) (i.v) were reported to be non-teratogenic. Taken together, there is no evidence or compelling pre-clinical data to state that Ondansetron is teratogenic in rats.

(*Id.* at 9).

As part of its submission, Novartis included the referenced Dr. Danielsson paper detailing the mechanism of action theory that is based in part on the Japanese animal studies. (*Id.* at 26). It also included English translations of those Japanese animal study publications. (*Id.*; GSK Suppl. SMF ¶ 51.b).

Novartis also referred to GSK's 2019 citizen petition in its letter to the FDA included with its PAS submission. (Hill Suppl. Decl., Ex. 190 at 1-2). It noted that although the citizen petition did not discuss the recently published epidemiological data, Novartis "acknowledge[d]

GSK's request that FDA review the four categories of information discussed within the Citizen Petition and take actions as the [FDA] deems appropriate." (*Id.*).

On November 6, 2020, the FDA responded to Novartis and included a redlined version of the Zofran labeling with explanatory comments. (*Id.*, Ex. 197). In the pregnancy "Risk Summary" section, the FDA rejected the proposed warning that "[t]he use of ondansetron in pregnancy is not recommended" and instead added: "[a]ll pregnancies have a background risk of birth defect, loss, or other adverse outcomes." (*Id.* at 6486). In its comments, the FDA explained that "[g]iven the available pharmacovigilance data, and the methodological limitations and the inconsistency in published epidemiology findings, one cannot determine that maternal ondansetron use increases the risk of major birth defects, miscarriage, or adverse maternal outcomes," so that "the available data do not support a recommendation to avoid Zofran in pregnancy." (*Id.*). It also deleted the proposed warning that "[i]n human epidemiological studies an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy," and instead added that "[p]ublished epidemiological studies on the association between ondansetron use and major birth defects have reported inconsistent findings and have important methodological limitations hindering interpretation." (*Id.* at 6485). In its comments, it explained that "[g]iven the inconsistency in published findings and the limitations in the design of [the epidemiological] studies, an increased risk of fetal orofacial clefts from maternal ondansetron use cannot be concluded." (*Id.*).

The FDA also removed in its entirety the proposed "Females and Males of Reproductive Potential" section, noting that "due to inconsistency in published findings and the limitations in the study designs, one cannot conclude that maternal exposure to ondansetron is associated with adverse developmental outcomes." (*Id.* at 6487). It also removed the proposed "Pregnancy and

Contraception" subsection in the "Patient Counseling Information" section and noted that "[w]e do not agree these precautions are warranted." (*Id.* at 6496).

The FDA did not propose any changes to the label's pregnancy "Risk Summary" section concerning animal studies or its animal data subpart within the pregnancy section. (*Id.* at 6485-87). It did propose one addition to the lactation section based on the results of animal studies to aid the prescriber in interpreting those studies. (*Id.* at 6487).

On November 16, 2020, Novartis responded to the FDA with further proposed changes to Zofran's labeling. (*Id.*, Exs. 216-218). In the pregnancy "Risk Summary" section, Novartis proposed the language that "based on the available data, the association of ondansetron administration during the first trimester of pregnancy with orofacial clefts in infants cannot be ruled out," and although it did not propose adding back the warning that the use of ondansetron in pregnancy is not recommended, it proposed adding the warning that the use of ondansetron in pregnancy "has not been evaluated in randomized, clinical studies." (*Id.*, Ex. 218 at 6639). It proposed deleting the line added by the FDA that "[a]t this time, there is no consistent evidence that ondansetron exposure in early pregnancy is associated with cleft palate." (*Id.* at 6640). It noted in a comment that it "reiterates that no causal role could be established between the [adverse] events and ondansetron, but considers the association from the available data is clinically significant." (*Id.* at 6632). Novartis did not propose to add back in the deleted "Females and Males of Reproductive Potential" section or the "Pregnancy and Contraception" subsection. (*Id.* at 6641, 6652).

Once again, Novartis did not propose any changes to the label's pregnancy "Risk Summary" section concerning animal studies or its animal data subpart within the pregnancy section. (*Id.* at 6639-40).

On January 15, 2021, in its denial of GSK's 2019 citizen petition, the FDA noted that Novartis's 2020 labeling supplement "remain[ed] under review." (Notice by Plaintiffs' Lead Counsel of FDA Denial of GSK's Citizen Petition, January 15, 2021, Ex. A at 2).

On March 25, 2021, the FDA responded to Novartis's November 16, 2020 revised labeling submission. (Notice by GSK of FDA's Labeling Revisions, April 2, 2021, Ex. A).[9] In the pregnancy "Risk Summary" section, the FDA removed Novartis's proposed additions that "based on the available data, the association of ondansetron administration during the first trimester of pregnancy with orofacial clefts in infants cannot be ruled out" and that "[t]he use of ondansetron in pregnancy has not been evaluated in randomized clinical studies." (*Id.* at 2027). In its comments, it explained that "given the inconsistent findings and methodological limitations of the published epidemiological studies" it was "not able to make any conclusions regarding the association between ondansetron use and major birth defects" or the "safety of ondansetron use in pregnancy." (*Id.*). In the human data section the FDA proposed the statement that "[a]vailable data on ondansetron use in pregnant women from several published epidemiological studies preclude an assessment of a drug-associated risk of adverse fetal outcomes due to important methodological limitations." (*Id.*). It did not propose any changes to the label's pregnancy "Risk Summary" section concerning animal studies or its animal data subpart within the pregnancy section. (*Id.* at 2027-28).

On April 6, 2021, Novartis accepted in full all of the FDA's March 25, 2021 proposals and revisions. (Notice by GSK re GSK's Notice of FDA's Labeling Revisions, April 16, 2021,

[9] It does not appear that GSK submitted an affidavit authenticating Exhibit A. However, it is not in dispute that the referenced exhibit is the FDA's March 25, 2021 response to Novartis's labeling revisions.

Exs. A-C).[10]

On April 29, 2021, the FDA informed Novartis that it formally approved the most recent version of the Zofran label—the one proposed by the agency on March 25, 2021—with one revision: in the label for the injectable formulation it added the word "oral" to one sentence in the pregnancy animal data subsection to identify how rats in a particular study received Zofran doses. (GSK's April 30, 2021 Notice of FDA's Approval of Updated Labeling, Exs. A-D).[11]

Thus, the currently approved label for Zofran states, in part:

> Risk Summary
>
> Published epidemiological studies on the association between ondansetron use and major birth defects have reported inconsistent findings and have important methodological limitations that preclude conclusions about the safety of ondansetron use in pregnancy *(see Data)*. Available postmarketing data have not identified a drug-associated risk of miscarriage or adverse maternal outcomes. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered intravenously during organogenesis at approximately 3.6 and 2.9 times the maximum recommended human intravenous dose of 0.15 mg/kg given three times a day, based on body surface area, respectively *(see Data)*.
>
> . . .
>
> *Animal Data*
>
> In embryo-fetal development studies in rats and rabbits, pregnant animals received intravenous[12] doses of ondansetron . . . during the period of organogenesis. With the exception of short periods of maternal weight loss and a slight increase in the incidence of early uterine deaths at the high dose level in rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring.
>
> . . . In an oral pre- and post-natal development study pregnant rats received oral doses of

[10] It does not appear that GSK submitted an affidavit authenticating Exhibits A, B, and C. However, it is not in dispute that the referenced exhibits are Novartis's April 6, 2021 response to the FDA's most recent labeling revisions.

[11] It does not appear that GSK submitted an affidavit authenticating Exhibits A, B, C, and D. However, it is not in dispute that the referenced exhibits are the FDA's April 29, 2021 approval of Novartis's prior approval supplement to Zofran's label.

[12] The label for the oral formulation of Zofran states that pregnant animals received oral doses of ondansetron in the study. (GSK's April 30, 2021 Notice of FDA's Approval of Updated Labeling, Ex. D at 8).

> ondansetron . . . . With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation.

(*Id.*, Ex. B at 8).

The parties agree that the April 29, 2021 letter from the FDA is a final agency action.

I. Plaintiffs' Allegations of Omissions in FDA Submissions

Plaintiffs do not dispute the labeling history outlined above. Nonetheless, they contend that GSK failed to disclose material evidence to the FDA concerning the safety of Zofran prior to its approval in 1991, and after it came on the market. Therefore, according to plaintiffs, the FDA's initial categorization of Zofran as a pregnancy category B drug, and its subsequent refusal to approve label warnings about its use by pregnant women, were based on incomplete information.

While plaintiffs identify a number of alleged omissions and mischaracterizations in GSK's submissions to the FDA, there are four primary categories of allegedly omitted evidence on which they rely: (1) results from three Japanese animal studies; (2) an accurate description of Zofran's biological mechanism of action; (3) adverse event data; and (4) information concerning GSK's involvement in the *Einarson* birth defect study.

1. Japanese Animal Studies

a. The Three Disputed Studies (100423, 100424, and 100441)

Between 1988 and 1990, GSK conducted animal reproduction toxicity studies in Japan through an affiliate, Nippon Glaxo. (Jenner Decl., Ex. A ("Danielsson Report") at 45-46). Three of the studies were labeled 100423, 100424, and 100441. Those three studies began in 1988, with final study reports completed on September 29, 1988 (100423), October 30, 1989 (100424), and December 19, 1990 (100441). (Hill Decl., Exs. 117-18, 120).

One of plaintiffs' experts, Dr. Bengt Danielsson, has prepared a report concluding that

the three studies found that Zofran had teratogenic effects. He bases his conclusion on increases in embryofetal death and incidences of major external malformations and skeletal defects in the Zofran-treated groups of rats and rabbits, as compared to untreated controls and historical control data. (Danielsson Report at 43, 45-46). GSK strongly disputes that conclusion.

Plaintiffs characterize Study No. 100423 as having "reported an increase in embryofetal death in the 10 mg/kg intravenous Zofran-treated group of rats compared to untreated controls." (Pls. CMF ¶ 2). GSK disputes "that the study showed an increase in embryofetal death in" that dosing group; it contends that the study investigators determined that "[o]n fetuses, no embryolethal, growth suppressive or teratogenic effects related to administration of [Zofran] were observed in any groups." (Def. Resp. ¶ 2; Hill Decl., Ex. 117 at 040).

Plaintiffs characterize Study No. 100424 as having "reported increases in embryonic death and increased incidences of major external malformations in the 10 mg/kg intravenous Zofran-treated group of rats compared to controls and historical control data, including ventricular septal defects among others." (Pls. CMF ¶ 2). GSK notes that Dr. Danielsson himself acknowledged that there was not a single external malformation observed in the study. (*See* Danielsson Report at 48-49). It further contends that the study investigators concluded the following:

> In the observation of fetuses (F1), there were no significant differences between the [Zofran] groups and the control group in either the number of live fetuses or dead implants ratio, indicating no fetal lethal effect of [Zofran] . . . . No external anomalies were observed, but skeletal and visceral anomalies or variations were observed with low incidences in [the Zofran groups]. However these incidences had no dose-dependency, and all of the changes were well known to occur spontaneously in rats. Consequently, [Zofran] was considered to have no teratogenicity.

(Hill Decl., Ex. 118 at 584).

Finally, plaintiffs characterize Study No. 100441 as having "reported an increase in some

skeletal defects, among others in the 2.5 and 10 mg/kg oral Zofran-treated groups of rabbits compared to untreated controls." (Pls. CMF ¶ 2). GSK notes Dr. Danielsson's statement that Study No. 100441's observations were "likely to be related to the observed decreased maternal body weight gain and absolute decreases in body weight, under certain periods in these studies, and not directly related to ondansetron exposure." (Danielsson Report at 56). It further contends that the study's "findings [of skeletal defects] do not indicate an increase in malformations or selective developmental toxicity," and that the study investigators concluded that the "[t]he effects of [Zofran] were not observed in the incidences of external, visceral or skeletal anomalies and variations in fetuses," and that "there were no findings indicating the teratogenicity of [Zofran]." (Hill Decl., Exs. 149 at 19; 120 at 415).

b. GSK's Disclosure of the Studies

Plaintiffs contend that GSK withheld the three Japanese animal studies from the FDA, and thus withheld animal reproduction data allegedly showing adverse effects on the fetus.

As noted, Zofran was initially approved on January 4, 1991. In 1992, seven Japanese-language reproductive toxicology studies of Zofran were published in peer-reviewed journals. The publications had English-language tables and data provided in Arabic-numeral format. Two of the three studies at issue were among that group. (Hill Suppl. Decl., Exs. 177-78; *see also* Hill Decl., Exs. 90-91).[13]

It is undisputed that GSK at least partly disclosed to the FDA the existence of Study Nos. 100423, 100424, and 100441 in its December 23, 1993 "Annual Report" letter. (Jenner Decl., Ex. B at 819-20). The Annual Report, submitted to the FDA pursuant to 21 C.F.R. § 312.33,

[13] Study No. 100423 was not included, as it was a preliminary study conducted "[t]o establish the dose levels" for the definitive Study No. 100424. (Hill Decl., Ex. 117 at 035). Study No. 100441 was also a definitive study. (*Id.*, Ex. 120).

provided the name and study number for each of the three studies, among other reproduction studies conducted on Zofran in Japan. (*Id.*). The disclosure was made under a sub-heading entitled "Studies performed specifically to satisfy Japanese regulatory requirements. These studies are either repetitive or provide no new significant safety information." (*Id.*).[14] GSK did not provide the FDA with copies of the studies themselves, which were only available in Japanese at that time. (*See* Def. Resp. ¶¶ 4-6).[15]

In a September 11, 1997 pharmacology review, the FDA, having reviewed another definitive Japanese study, Study No. 100422, concluded that Zofran "was not teratogenic in the F0 generation. Furthermore, there were no treatment-related effects on the reproductive performance of the F1 generation." (Hill Decl., Ex. 59 at 191). The FDA also noted that "[t]hese results are comparable" to those of a similar study that was included with the original submission for Zofran. (*Id.*).

On October 29, 2014, in connection with a request for GSK to update the pregnancy section of the Zofran label to conform with the Physician Labeling Rule (PLR) format, the FDA requested that GSK "provide full details of animal reproduction studies" of Zofran. (Jenner Decl., Ex. M at 074).

GSK responded to that request on March 3, 2015, stating that it was providing "full details of animal reproduction studies as requested." (*Id.*, Ex. N at 712). GSK's response described animal reproduction studies, identified individual study report numbers, and explained that "[t]hese reports were contained in [an October 12, 1989 NDA submission]." (*Id.*). Plaintiffs

[14] Each Japanese study mirrored a study performed by GSK in the United Kingdom that used the same animal and method of administration of Zofran. (GSK Mem. at 14). GSK submitted the studies from the United Kingdom as part of the 1991 Zofran approval. (Hill Decl., Ex. 58 at 903-08).

[15] As of 1995 the two definitive studies were identified in Toxnet, a free database maintained by the National Institutes of Health. (Hill Decl., Ex. 71 at 2; Exs. 90-91).

contend that the response failed to disclose any information about the three Japanese animal studies, which were "animal reproduction studies" that fell within the scope of the October 29, 2014 information request. (Pls. CMF ¶ 22).

In its October 27, 2015 denial of the Reichmann citizen petition, the FDA noted that Zofran animal reproduction studies conducted as part of GSK's safety evaluation of Zofran were "relevant to this Petition." (Hill Decl., Ex. 32 at 12). The denial specifically cited a summary of data written in 1989 by Dr. Tucker, a GSK employee. (*See id.*; Jenner Decl., Ex. O at 751). The summary did not include a discussion of Japanese animal studies. (Jenner Decl., Ex. O at 751). In its denial of the petition the FDA noted that the studies discussed in the Tucker article "did not show any evidence of impaired fertility or harm to the fetus due to ondansetron." (Hill Decl., Ex. 32 at 12). According to GSK, the Tucker paper was just one of a number of sources of information the FDA specifically considered before denying the petition, including one case-control study, four cohort studies (including a 2014 paper co-authored by Dr. Danielsson), and one case series. (*Id.* at 7-12).[16]

Plaintiffs contend, however, that GSK was aware of the citizen petition, but failed to provide any information to the FDA about the Japanese reproduction studies in response. (Pls. CMF ¶ 27). GSK counters that it was not obligated to respond (and therefore did not do so), as the FDA never contacted them in connection with the citizen petition. (Def. Resp. ¶ 27 (citing Hill Decl., Ex. 145 ("Rebar Dep.") at 313)).

GSK attached full English translations of all three study reports to its 2019 citizen petition submitted to the FDA. (Hill Suppl. Decl., Exs. 165-66, 169). It also attached translated

[16] The FDA also indicated that it considered "information submitted by [GSK] to support approval of the ondansetron NDA," "post-marketing drug and device adverse event data," and scientific literature obtained through public submissions and through its own "targeted searches." (Hill Decl., Ex. 32 at 18 n.56).

versions of the peer-reviewed Japanese publications that discussed Study Nos. 100424 and 100441, as well as Study No. 100422. (*Id.*, Exs. 176-78).

In its 2020 PAS, Novartis also attached the English translations of the Japanese publications that discussed Study Nos. 100424 and 100422. (*Id.*, Ex. 193 at 9, 28; Exs. 194-95). In its clinical overview Novartis discussed those two studies and noted that "no embryo toxicity was observed" in them. (*Id.*, Ex. 193 at 9).

2. Biological Mechanism of Action

Plaintiffs further allege that GSK "failed to disclose to [the] FDA an accurate description of Zofran's potential to cause embryonic arrhythmias with a resulting biological mechanism of teratogenicity." (*See* Pls. Resp. ¶ 22). The disputed mechanism of action is alleged to cause fetal heart defects when Zofran "inhibits hERG potassium channels" and disrupts cardiac rhythm. (Pls. CMF ¶¶ 11-18).

Plaintiffs contend that GSK became aware of the hERG channel mechanism by at least 2002, but failed to disclose or properly explain it to the FDA. (*Id.* ¶¶ 15-17). GSK contends that the hERG channel mechanism is merely a hypothesis, is not supported by evidence, and, regardless, that the FDA considered evidence of the mechanism of action and still concluded there was insufficient data to support a pregnancy warning. (Def. Resp. ¶¶ 15-17, 19).

a. Evidence of the Mechanism of Action and GSK's Knowledge

In 1994, F.G. de Lorenzi *et al.* published a study in the British Journal of Pharmacology titled "Block of the delayed rectifier current (IK) by the 5-HT3 antagonists ondansetron and granisetron in feline ventricular myocytes." (Jenner Decl., Ex. C). According to plaintiffs, the study reported that Zofran inhibits hERG potassium channels, which is the mechanism of action by which Zofran can cause QT prolongation—a condition they characterize as a serious disturbance of the heart's rhythm. (Pls. CMF ¶ 11). GSK contends, however, that the study did

not report that Zofran inhibits hERG potassium channels, did not specifically investigate hERG potassium channels, and was not an investigation of the effects of Zofran on QT interval in humans. (Def. Resp. ¶ 11). Moreover, it disputes the characterization of QT prolongation as a "serious" disturbance of the heart's rhythm. (*Id.*).

In 2000, Yuri Kuryshev *et al.* published a study in the Journal of Pharmacology and Experimental Therapeutics titled "Interactions of 5-hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels." (Jenner Decl., Ex. D). Plaintiffs contend that the study similarly reported that Zofran was associated with QT prolongation due to its inhibition of hERG potassium channels. (Pls. CMF ¶ 12). GSK, however, disputes that finding and contends that the study was not designed to examine the effect of Zofran on QT prolongation in humans. (Def. Resp. ¶ 12).[17]

In 2002, an internal GSK document reported that drugs that reduce the embryonic heart rate and produce heart rhythm abnormalities are likely to cause embryonic death that "is likely to result from drug induced bradycardia which impairs circulation and leads to hypoxia causing embryonic malformations/death." (Jenner Decl., Ex. U at 707). The document cited a 1994 paper co-authored by Dr. Danielsson. (*Id.*). Plaintiffs contend that this explanation of the "biological mechanism of teratogenicity arising from drug-induced bradycardia, i.e., arrhythmia," is "virtually identical" to the explanation provided by Dr. Danielsson with reference to Zofran in his expert report in this litigation, implying that GSK was aware of the mechanism

[17] After the publication of the study, GSK's then-Director of Safety Pharmacology referred to the study as a "sound piece of work . . . from a respected group." (Jenner Decl., Ex. T at 013). The director noted that the study showed that "ondansetron can inhibit current flow through cloned human cardiac ion channels and therefore has the potential to affect cardiac repolarisation." (*Id.*). However, the director went on to note that "the evidence [GSK had] that ondansetron causes QT prolongation (a measure of cardiac repolarisation) is not very convincing," and that "the clinical relevance of the non-clinical finding referred to [by the Kuryshev study] is uncertain." (*Id.*).

in 2002. (Pls. CMF ¶ 16; Danielsson Report at 4).[18]

GSK, however, contends that "[t]he mechanism discussed [in the document] does not apply to ondansetron, nor does [it] necessarily apply to every drug that may have an effect on hERG channels or heart rhythm." (Def. Resp. ¶ 16). It contends that it "never determined that Zofran could cause birth defects of any kind by the mechanism discussed" in the document, and that "there was no finding supporting a treatment-related effect on embryolethality, or any finding of teratogenicity, reported in any of the Zofran reproductive toxicity studies." (*Id.*). Finally, it contends that Dr. Danielsson's mechanism is merely hypothetical, and that his opinions are not reliable, adequately supported, or admissible. (*Id.* ¶ 18).

b. The FDA's Awareness of the Mechanism of Action

GSK first contends that it identified both the 1994 de Lorenzi and 2000 Kuryshev studies in a 2005 submission to the FDA. (Hill Decl., Ex. 103 at 4460). In addition, GSK notes that it cited Dr. Danielsson's 2014 paper that described the mechanism of action theory in an annual report submitted to the FDA in 2015. (*Id.*, Ex. 95 at 4793).

In its denial of the 2013 Reichmann citizen petition, the FDA spent a page discussing the 2014 Danielsson study. (*Id.*, Ex. 32 at 10-11).[19] It stated that "given the limitations of the [study], as well as the lack of consistent evidence for cardiovascular teratogenicity the study does not support a change in pregnancy risk category." (*Id.* at 13). It further noted that "[p]revious published studies have not reported increased associations between ondansetron use in early pregnancy and atrial and/or septal cardiovascular malformations, and the signal for

[18] Plaintiffs also point to language from GSK's 2011 Lamictal label as further evidence of its knowledge of the mechanism of action. (Pls. CMF ¶ 17; Jenner Decl., Ex. V).

[19] A third-party also submitted a comment to the petition, which described the same alleged mechanism of action. (Hill Decl., Ex. 30).

cardiovascular malformations reported by Danielsson et al. may or may not be causal." (*Id.* at 11). The FDA also discussed the already-acknowledged possibility of QT prolongation in the patient *taking* Zofran, and noted that that was "already clearly identified on current ondansetron labeling as potential adverse reactions for health care providers to consider before treating any patient with ondansetron, whether pregnant or not." (*Id.* at 16).

In its September 2015 submission to the FDA, Novartis's clinical overview described, among other sources, Dr. Danielsson's 2014 paper and one of his publications from 2007. It characterized the papers as hypothesizing that "congenital heart defects could be related to the potential for ondansetron to cause QT prolongation and cardiac arrhythmias" and as having found that "hERG channel blockade could induce developmental toxicity generally due to embryonic heart arrhythmias leading to transient hypoxia and reperfusion injuries." (*Id.*, Ex. 34 at 38). However, after an extensive review of the literature, Novartis discounted the proposed mechanism based, at least in part, on its understanding at the time that the results of Zofran reproduction studies conducted in the United Kingdom did not indicate an increased risk of embryonic death or malformations. (*Id.*; Pls. CMF ¶ 24; Def. Resp. ¶ 24). The FDA ultimately rejected Novartis's request to add a pregnancy warning in 2016, based, in part, on the fact that it found "no evidence, nonclinical or mechanism of action, that raises concerns for adverse fetal outcomes with Zofran." (Hill Decl., Ex. 39 at 451).

In its 2019 citizen petition, GSK described to the FDA the theory that "ondansetron has the potential to cause QT prolongation and cardiac arrythmias, which can interrupt blood and oxygen supply to the embryo and cause birth defects." (*Id.*, Ex. 160 at 8). GSK submitted as exhibits to the petition Dr. Danielsson's 2014 and 2018 publications discussing the mechanism of action. (*Id.*, Ex. 161 at 2). It also submitted the 1994 de Lorenzi and 2000 Kuryshev studies.

(*Id.* at 3-4). Plaintiffs, as part of their presentation to the FDA in response to the citizen petition, submitted Dr. Danielsson's July 5, 2018 expert report in this case, his August 27, 2018 rebuttal expert report in this case, and his October 12, 2018 deposition in this case. (*Id.*, Ex. 208 at 1). All three discuss the disputed mechanism of action. (*See* Danielsson Report; Hill Suppl. Decl., Exs. 211-12).

In its June 2020 submission to the FDA, Novartis included a description of Dr. Danielsson's 2018 publication detailing the mechanism of action. (*Id.*, Ex. 193 at 9). Novartis acknowledged Dr. Danielsson's "mechanistic explanation" of teratogenicity in rat embryos in vitro based on the Japanese animal studies, but noted that no "embryo toxicity was observed" in the studies themselves. (*Id.*). Thus, Novartis concluded that the "teratogenicity of ondansetron referenced by [Dr. Danielsson] from" the Japanese animal studies "is questionable and does not provide clear evidence of teratogenic potential," and that "there is no evidence or compelling pre-clinical data to state that Ondansetron is teratogenic in rats." (*Id.*).

Neither Novartis nor the FDA proposed any substantive changes to the animal data section of Zofran's label as a result of the PAS. (*Id.*, Exs. 192, 197, 218; GSK's April 2, 2021 Notice of FDA's Labeling Revisions, Ex. A; GSK's April 16, 2021 Addendum to its Notice of FDA's Labeling Revisions, Ex. B; GSK's April 30, 2021 Notice of FDA's Approval of Updated Labeling, Ex. A). In its initial response to Novartis, the FDA included a comment indicating that it was relying, in part, on Dr. Danielsson's 2014 paper for its revisions to the human data section of the pregnancy portion of the label. (Hill Decl., Ex. 218 at 6640).

3. Adverse Event Data

Plaintiffs also allege that beginning in 2005, GSK failed to disclose, or incorrectly coded, certain adverse event reports and failed to include those reports in the Zofran safety database, thereby excluding them from the data analysis provided to the FDA.

a. GSK's 2005 Adverse Event Coding and 2014 Disproportionality Analysis

Under FDA regulations, a drug manufacturer is required to fully disclose all "adverse event" data it receives about the use of the drug in humans, both during the NDA process and afterward. *See* 21 C.F.R. §§ 314.50(f)(2) ("The NDA is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo [{unless this requirement is waived}]."); 314.50(d)(5)(vi)(b) ("The applicant must . . . update periodically its pending NDA with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling . . . . These 'safety update reports' must include . . . the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event {unless this requirement is waived}."); 312.33 (requiring annual reports for investigational NDAs that include a summary of "[i]nformation obtained during the previous year's clinical and nonclinical investigations, including . . . [a] narrative or tabular summary showing the most frequent and most serious adverse experiences by body system . . . [and a] list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.").[20]

GSK coded adverse events involving Zofran using the Medical Dictionary for Regulatory Activities (MedDRA) terms, which provide five levels of medical coding hierarchy, the most general of which is the System Organ Class ("SOC"). (Jenner Decl., Ex. W).

[20] The regulations define an "adverse event" as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." 21 C.F.R. § 312.32(a).

Plaintiffs contend that in a 2005 report summarizing pediatric events involving Zofran, GSK categorized cardiac-related congenital adverse events under six separate SOCs: (1) cardiac disorders; (2) congenital, familial, and genetic disorders; (3) general disorders and administration site concerns; (4) injury poisoning and procedural complications; (5) nervous system disorders; and (6) respiratory, thoracic, and mediastinal disorders. (Pls. CMF ¶ 29 (citing Jenner Decl., Ex. Y)). They further contend that in 2014, GSK responded to an FDA request for data on Zofran use in pregnancy with a disproportionality analysis ("DPA") on only two SOCs: (1) cardiac disorders and (2) pregnancy, puerperium, and perinatal conditions. (Pls. CMF ¶¶ 30-31, (citing Jenner Decl., Ex. Z at 150, 165)). Plaintiffs allege this "limited analysis necessarily undercount[ed] the reporting of congenital cardiac adverse events that were categorized under other SOCs," such that an increased risk of birth defects would not be detected in the summary provided to the FDA. (Pls. Mem. at 35).

GSK has responded to that claim in a number of ways. First, it denies that the adverse event reports in question were miscoded. Second, it disputes that the 2014 DPA was ever sent to the FDA. Third, it contends that it regularly supplied the FDA with detailed information about pregnancy-related events, not just coded lists and DPAs.[21] In particular, it identifies its 2011 safety report submitted to the FDA in which it retrieved 765 Zofran-related reports and provided a detailed summary of the reported anomalies. (GSK Mem. at 21; Hill Decl., Ex. 27 at 4313-19). It also notes that Novartis continued to submit adverse event reports to the FDA after it obtained control of Zofran: for example, in 2015 Novartis retrieved 1,028 Zofran-related reports from

[21] GSK also notes that the FDA maintains its own database of adverse event reports that healthcare professionals, consumers, and manufacturers submit to it: the FDA Adverse Event Reporting System ("FAERS"). (Hill Decl., Ex. 50 at 1). The database "is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products." (*Id.*).

GSK's safety database and presented them to the FDA. (GSK Mem. at 22; Hill Decl., Ex. 34 at 19-36). Fourth, it contends that plaintiffs are unable to show that some other kind of coding would have demonstrated an increased risk. Finally, it contends that the FDA considered and rejected pregnancy warnings after discounting the value of adverse event reports, finding them not significant in part given the background incidence rate of heart defects. (*See* Hill Decl., Ex. 39 at 450, 465) ("[W]e do not believe that there is any basis to suspect drug attribution to [reported] congenital malformations cases for them to qualify as 'adverse reactions.' Only adverse reactions, where there is some basis to believe that the drug plays a role in the adverse outcome, should be included in labeling . . . .") (the FDA's rejection of adding a pregnancy warning in Novartis's 2015 PAS); (*Id.*, Ex. 32 at 13) ("[T]he additional information we reviewed (e.g., results of an independent literature search and adverse event reports) does not provide evidence of a safety concern related to the use of ondansetron during pregnancy.") (the FDA's rejection of the 2013 Reichmann citizen petition).

4. The *Einarson* Birth Defect Study

Plaintiffs further allege additional omissions concerning the so-called *Einarson* study. According to plaintiffs, "GSK directed [the] FDA, treating physicians, and the rest of the medical community to a small, prospective 2004 study that the company claimed established Zofran's safety for use during pregnancy." (Pls. Mem. at 36). The study, entitled "The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study," was by Adrienne Einarson *et al.*, and was published in September 2004. (Jenner Decl., Ex. HH).

Plaintiffs allege that "GSK failed to disclose its involvement in editing and advising" that study, and that the FDA relied on it "as evidence that Zofran was non-teratogenic." (Pls. Mem. at 6 (citing Jenner Decl., Ex. F at 358)). They further allege that GSK "chose to stay silent on an unreported birth defect in the study group[,] as well as the opinions of top GSK scientists that the

study it helped bring to light was incredibly flawed and insufficiently powered." (Pls. Mem. at 6 (citing Jenner Decl., Exs. G, H)).

GSK contends that the study is irrelevant to the preemption analysis because the FDA reviewed the *Einarson* data in its labeling approval process. (Def. Reply Mem. at 26-28; Def. Resp. ¶¶ 33, 35 (citing Jenner Decl., Ex. I at 913-14)). The FDA observed in its denial of the 2013 Reichmann citizen petition that "the study was of limited size and statistical power." (Hill Decl., Ex. 32 at 9). Novartis also discussed the study in its clinical overview submitted with its 2015 PAS. (*Id.*, Ex. 34 at 8). In addition, in response to Novartis's 2020 PAS, the FDA indicated that it was not relying on the study to support the information included in Zofran's label. (*Id.*, Ex. 218 at 6640, 6653).

GSK also alleges that it did not hide its involvement in the study because in the "Acknowledgements" section, the study notes it was "supported by an unrestricted grant from" GSK. (*Id.*, Ex. 73 at 942). GSK also contends that the "unreported birth defect" in the study group was omitted because it did not qualify as a "major malformation," what the study intended to capture, and that nonetheless the event itself was reported to the FDA as an adverse event in its 2011 submissions to the agency. (GSK Mem. at 48; Hill Decl., Ex. 27 at 4315).

III. Legal Standard

The role of summary judgment is "to pierce the pleadings and to assess the proof in order to see whether there is a genuine need for trial." *Mesnick v. Gen. Elec. Co.*, 950 F.2d 816, 822 (1st Cir. 1991) (quoting *Garside v. Osco Drug, Inc.*, 895 F.2d 46, 50 (1st Cir. 1990)). Summary judgment shall be granted when "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). A genuine issue is "one that must be decided at trial because the evidence, viewed in the light most flattering to the nonmovant, would permit a rational factfinder to resolve the issue in favor of either party."

Medina-Munoz v. R.J. Reynolds Tobacco Co., 896 F.2d 5, 8 (1st Cir. 1990) (citation omitted). In evaluating a summary judgment motion, the court indulges all reasonable inferences in favor of the nonmoving party. *See O'Connor v. Steeves*, 994 F.2d 905, 907 (1st Cir. 1993). When "a properly supported motion for summary judgment is made, the adverse party must set forth specific facts showing that there is a genuine issue for trial." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 250 (1986) (quotations omitted). The nonmoving party may not simply "rest upon mere allegation or denials of his pleading," but instead must "present affirmative evidence." *Id.* at 256-57.

IV. Analysis

A. FDA Preemption Generally

"A fundamental principle of the Constitution is that Congress has the power to preempt state law." *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 (2000) (citations omitted). "Federal law preempts state law (1) when Congress has expressly so provided, (2) when Congress intends federal law to 'occupy the field' and (3) to the extent that state law conflicts with any federal statute." *Am. Steel Erectors, Inc. v. Loc. Union No. 7, Int'l Ass'n of Bridge, Structural, Ornamental & Reinforcing Iron Workers*, 536 F.3d 68, 84 (1st Cir. 2008) (citing *Crosby*, 530 U.S. at 372-73). This matter concerns "conflict" or "obstacle" preemption, which occurs when "compliance with both federal and state regulations is a physical impossibility" or when "the challenged state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Arizona v. United States*, 567 U.S. 387, 399 (2012) (internal quotation marks and citations omitted); *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011).

The preemption analysis here begins with the Supreme Court's decision in *Wyeth v. Levine*, 555 U.S. 555 (2009). In *Wyeth*, the court addressed whether state law failure-to-warn

claims against a drug manufacturer were preempted by federal law where the FDA had previously approved the drug's warning label. Because CBE regulations permitted the manufacturer to strengthen its warning unilaterally, the court found it could not conclude that it was impossible for the drug manufacturer to comply with both federal and state labeling requirements, "absent clear evidence that the FDA would not have approved a change" to the label. *Id.* at 571-73.

The Supreme Court reiterated the *Wyeth* "clear evidence" standard in *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 623-24, 624 n.8 (2011). Although the *PLIVA* court held that federal law preempted plaintiffs' claims under state laws, it did so by distinguishing *Wyeth*. *Id.* The court observed that unlike in *Wyeth*, where the CBE process made it possible for the manufacturer to comply with both federal and state law, the generic manufacturer in *PLIVA* could not act unilaterally; it had to obtain permission from the FDA before it could satisfy state law. *Id.* In such a case, the court held, it was impossible for the manufacturer to comply with both federal and state law, and therefore the state-law claims were preempted. *Id.* "The [*PLIVA*] Court thus limited *Wyeth* to situations in which the drug manufacturer can, 'of its own volition, . . . strengthen its label in compliance with its state tort duty.'" *In re Celexa & Lexapro Mktg. & Sales Pracs. Litig.*, 779 F.3d 34, 41 (1st Cir. 2015) (quoting *PLIVA*, 564 U.S. at 624). In other words, "[t]he line *Wyeth* and *PLIVA* thus draw [is] between changes that can be independently made using the CBE regulation and changes that require prior FDA approval." *Celexa*, 779 F.3d at 41. A manufacturer can use the CBE process only when "newly acquired information" reflects a "clinically significant hazard." 21 C.F.R. §§ 201.57(c)(6)(i), 314.70(b)(2)(iii).

In *Merck Sharpe & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019), the Supreme Court

answered two questions on how to decide *Wyeth* preemption that had divided lower courts.[22]

First, the *Albrecht* 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." *Id.* at 1679-81.[23] When deciding that legal question of what satisfies the "clear evidence" standard, the court said, "the judge must simply ask himself or herself whether the relevant federal and state laws irreconcilably conflic[t]." *Id.* at 1679 (quoting *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982)). The court then explained what such a conflict would look like:

> In a case like *Wyeth*, showing that federal law prohibited the drug manufacturer from adding a warning that would satisfy state law requires the drug manufacturer to show that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning.

Albrecht, 139 S. Ct. at 1678. Thus, *Albrecht* set forth a "two-prong test" for *Wyeth* preemption: "[a] drug manufacturer must demonstrate that (1) 'it fully informed the FDA of the justifications for the warning required by state law' and (2) 'the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning.'" *In re Avandia Mktg., Sales & Prods. Liab. Litig.*, 945 F.3d 749, 758 (3d Cir. 2019) (quoting *Albrecht*, 139 S. Ct. at 1678).

In discussing the second prong, the court noted that "the only agency actions that can determine the answer to the pre-emption question . . . are agency actions taken pursuant to the

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[22] Notably, the *Albrecht* court did not address *PLIVA* preemption. In *Albrecht*, the defendant "conceded that the FDA's CBE regulation would have permitted [it] to try to change the label to add a warning before 2010, but [it] asserted that the FDA would have rejected that attempt." *Albrecht*, 139 S. Ct. at 1675.

[23] This Court had previously held that *Wyeth* preemption was a question of fact for the jury, *In re Zofran (Ondansetron) Prods. Liab. Litig.*, 368 F. Supp. 3d 94, 116-17 (D. Mass. 2019), as had at least one federal court of appeals, *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 852 F.3d 268, 286, 289-91 (3d Cir. 2017). *See also In re Incretin-Based Therapies Prods. Liab. Litig.*, 721 F. App'x 580, 584 (9th Cir. 2017).

FDA's congressionally delegated authority." *Albrecht*, 139 S. Ct. at 1679 (citing *New York v. FERC*, 535 U.S. 1, 18 (2002)). It then described the processes by which federal law "permits" the FDA to communicate its disapproval of a warning: (1) "by means of notice-and-comment rulemaking setting forth labeling standards"; (2) "by formally rejecting a warning label that would have been adequate under state law"; or (3) "with other agency action carrying the force of law." *Albrecht*, 139 S. Ct. at 1679.

Second, the *Albrecht* court addressed how to decide factual questions that may arise. The court concluded that it would "not further define *Wyeth*'s use of the words 'clear evidence' in terms of evidentiary standards" because the "critical question" was a matter of law, not fact. *Id.*; *see also id.* at 1685 (Alito, J., concurring) ("First, although the Court's discussion of the point is a bit opaque, the Court holds—correctly, in my view—that *Wyeth*'s use of the phrase 'clear evidence' was merely a rhetorical flourish."). The court acknowledged, however, "that sometimes contested brute facts will prove relevant to a court's legal determination about the meaning and effect of an agency decision." *Id.* at 1680 (majority opinion). The court offered an example of such facts that is relevant here:

> For example, 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. Yet in litigation between a drug consumer and a drug manufacturer (which will ordinarily lack an official administrative record for an FDA decision), the litigants may dispute whether the drug manufacturer submitted all material information to the FDA.

Id. Because such "factual questions [are] subsumed within an already tightly circumscribed legal analysis," the *Albrecht* court held that they are "part and parcel of the broader legal question" and thus fit for resolution by a judge. *Id.* (citing *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 327 (2015)).

In a concurrence, Justice Thomas appeared to eliminate the first step of clear evidence preemption. He asserted that, if proper agency actions or other federal law prohibited the drug manufacturer from satisfying state law, "state law would be pre-empted . . . regardless of whether the manufacturer 'show[ed] that it fully informed the FDA of the justifications for the warning required by state law.'" *Albrecht*, 139 S. Ct. at 1683 n.* (Thomas, J., concurring) (quoting *id.* at 1678 (majority opinion)). He further emphasized that a defendant could point only to statutes, regulations, or other agency actions with the force of law to show that they were so prohibited. *Id.* at 1683 (Thomas, J., concurring) (noting that only "federal standards and policies that are set forth in . . . the statutory text that was produced through the constitutionally required bicameral and presentment procedures" can support preemption). He opined that a "complete response" letter by the FDA to a manufacturer that found its proposed label changes to be inadequate and that asked it to take further steps could not have a preclusive effect because FDA regulations state that those letters have "no implication as to the ultimate approvability" of the label changes, and therefore are not "final agency action with the force of law." *Id.* at 1682-83. Similarly, other informal agency communications or "hypothetical future rejections" based on a manufacturer's belief that a change would be rejected are not adequate evidence of preemption. *Id.*

In a concurrence joined by Chief Justice Roberts and Justice Kavanaugh, Justice Alito asserted that the second step of clear-evidence preemption does *not* require that the FDA "in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Id.* at 1678 (majority opinion). Specifically, Justice Alito pointed to a statutory provision passed after the events in *Wyeth*, 21 U.S.C. § 355(o)(4)(A), which "has imposed on the FDA a duty to initiate a label change '[i]f the Secretary becomes aware of new

information, including any new safety information . . . that the Secretary determines should be included in the labeling of the drug.'" *Albrecht*, 139 S. Ct. at 1684 (Alito, J., concurring) (quoting 21 U.S.C. § 355(o)(4)(A)). That statute did not "require the FDA to communicate to the relevant drug manufacturer that a label change is unwarranted; instead, the FDA could simply consider the new information and decide not to act." *Id.* Therefore, Justice Alito concluded, regardless of whether the FDA communicated its decision to the manufacturer, "if the FDA declines to require a label change despite having received and considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified." *See id.* FDA inaction in the face of 21 U.S.C. § 355(o)(4)(A) thus constitutes an appropriate agency action for consideration in the preemption analysis. Further, Justice Alito also stated that informal communication between the FDA and drug manufacturers should be considered in the preemption analysis. *See id.* at 1685 (including in his discussion of the relevant facts that the "FDA remained in contact with" the defendant about the issue).

In summary, under *Wyeth* and *PLIVA*, a drug manufacturer may prevail on a preemption defense if (1) the CBE process was not available, and therefore it could not make unilateral changes to the label, or (2) it establishes by "clear evidence" that the FDA would not have approved the changes to the label that the plaintiffs contend should have been made. Under *Albrecht*, that second question—whether there is "clear evidence" that the FDA would have rejected the proposed change—is a matter of law for the judge to decide, and it has two parts. A drug manufacturer must show both (1) that "it fully informed the FDA of the justifications for the warning required by state law"; and (2) that "the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *See Albrecht*, 139 S. Ct. at 1678.

Since *Albrecht*, several appellate decisions have addressed the preemption issues outlined by the Supreme Court. In *Avandia*, the Third Circuit found that *Albrecht* held that "in order to prove impossibility preemption, the drug manufacturer must show that the 'FDA would not approve changing the drug's label' and that the FDA was 'fully informed . . . of the justifications for the proposed warning' *at the time that the FDA rejected the proposed warning*." 945 F.3d at 759 (quoting *Albrecht*, 139 S. Ct. at 1678). Applying that test, the court found that a defendant had not shown that it had fully informed the FDA of the justifications for the warning required by state law, because the FDA indicated that it found the data submitted by the defendant with the proposed warning to be "inadequate," found the application to be "deficien[t]," and had requested more data. *Avandia*, 945 F.3d at 758. The court noted that the defendant could not rebut that conclusion by asserting that the information requested by the FDA was immaterial and thus the FDA was "fully informed" because the FDA, not the defendant, "can determine what information is 'material' to *its own* decision to approve or reject a labelling change." *Id.* at 759. At the second step, the court found that the FDA rejected the proposed warning because it contained various "deficiencies" that the FDA wanted the defendant to fix prior to it making a final determination, not because it determined that the warning was not needed. *Id.* at 759-60. Thus, the FDA did not inform the defendant that it "would not approve changing the drug's label to include [the relevant] warning." *Id.* at 759 (quoting *Albrecht*, 139 S. Ct. at 1678). Finally, the court noted that an informal phone conversation with an FDA official is not an appropriate agency action for preemption purposes under *Albrecht*. *Avandia*, 945 F.3d at 760.

In *Dolin v. GlaxoSmithKline LLC*, 951 F.3d 882 (7th Cir. 2020), the Seventh Circuit determined that a state-law claim was preempted because (1) a defendant fully informed the FDA of all relevant data underlying a label warning; (2) the FDA rejected the proposed warning;

(3) the FDA's rejection was a formal agency action "taken pursuant to the FDA's congressionally delegated authority"; and (4) the plaintiff failed to show that the defendant acquired new information after the FDA rejected its proposed warning that would have required the defendant to attempt another label change. *Id.* at 891 (quoting *Albrecht*, 139 S. Ct. at 1679).

In *Cerveny v. Aventis, Inc.*, 855 F.3d 1091 (10th Cir. 2017), decided before *Albrecht*, the Tenth Circuit had found that the FDA's rejection of a citizen petition "present[ing] arguments virtually identical to" the plaintiffs' constituted clear evidence that the FDA would have rejected a proposed label change under *Wyeth*. *Id.* at 1101. The court rejected the argument that the FDA "affords greater deference to label changes proposed by manufacturers than by citizens" as a reason to not consider the FDA's rejection of a citizen petition to be "clear evidence," and declined to impose a bright-line rule that citizen petitions could never constitute such "clear evidence" of the FDA's unwillingness to add a warning. *Id.* at 1102-03. After *Albrecht* was decided, the court declined to change its analysis, rejecting the argument that *Albrecht* requires that only labeling changes sought by the manufacturer can lead to preemption. *See Cerveny v. Aventis, Inc.*, 783 F. App'x 804, 808 n.9 (10th Cir. 2019).[24] It noted that "*Albrecht* prefaced its requirement that '[the drug manufacturer] fully informed the FDA of the justifications for the warning required by state law' as applying '[i]n a case like *Wyeth*' and noted that 'in *Wyeth*, [the Court] confronted [the impossibility-preemption question] in the context of a particular set of circumstances.'" *Id.* (quoting *Albrecht*, 139 S. Ct. at 1678). It concluded that the set of circumstances in its case had a key difference from those in *Wyeth*:

> In *Wyeth*, the Court needed to decide whether Wyeth was entitled to impossibility preemption based on the FDA's having earlier approved a drug label not warning of the

[24] In 2017 the Tenth Circuit had remanded the claims that were not preempted to the district court; in 2019, the court reviewed the district court's grant of summary judgment to the defendant on those claims. *Cerveny v. Aventis, Inc.*, 783 F. App's 804, 805 (10th Cir. 2019).

> specific dangers posed by the IV-push method of administering the drug. In *Wyeth*'s particular set of circumstances, the Court evaluated whether Wyeth had shown "clear evidence" that the FDA would have rejected the plaintiff's proposed label change warning of a risk from using the IV-push method of administering [the drug]. The Court concluded that Wyeth had failed to make this showing, noting in part that Wyeth had not shown that it had "supplied the FDA with an evaluation or analysis concerning the specific dangers posed by the IV-push method." Here, [the defendant] argues a different ground to show that the FDA would have rejected the [plaintiffs'] proposed warning. Unlike Wyeth, [the defendant] is not left to show clear evidence that the FDA would have rejected any unilateral label change under the CBE regulation, but [the defendant] has a separate avenue—the FDA's unequivocally having rejected [the] citizen petition advocating for the warning that the [plaintiffs] now assert.

Id. (internal citations omitted). It asserted that there was nothing in *Wyeth* or *Albrecht* "excluding [the defendant] from justifying preemption on this basis." *Id.*[25]

B. Whether Preemption is An Affirmative Defense

One question that remains open after *Albrecht* is whether preemption is an affirmative defense, as to which the manufacturer bears the burden of proof. This Court previously determined that the answer is yes. *In re Zofran (Ondansetron) Prods. Liab. Litig.*, 368 F. Supp. 3d at 114.

Courts elsewhere have decided otherwise. The court in *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644 (S.D.N.Y. 2017) adopted a two-stage burden-shifting framework:

> First, the plaintiff must show that there existed "newly acquired information" such that the defendants could unilaterally change the label pursuant to the CBE regulation without FDA approval. But, the mere availability of a CBE label amendment does not necessarily defeat a manufacturer's preemption defense. Because the FDA "retains the authority to reject labeling changes," a manufacturer may still—even after the plaintiff has identified "newly acquired

[25] In *Knight v. Boehringer Ingelheim Pharms., Inc.*, 984 F.3d 329 (4th Cir. 2021), the Fourth Circuit described how a manufacturer can demonstrate that the CBE process was not available because it had no "newly acquired information." *See id.* at 332. The court found that the manufacturer was not in possession of any newly acquired information about a causal association between the drug and a risk of harm, and thus it could not unilaterally change the drug's label. *Id.* at 341. Thus, the plaintiffs' claims were preempted. *Id.* It emphasized that a manufacturer must be in possession of information that "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA," and must show "evidence of a causal association" between the drug and the harm. *Id.* at 338 (citing 21 C.F.R. §§ 314.3(b), 314.70(c)(6)(iii)(A)).

> information"—establish an impossibility preemption defense through "clear evidence that the FDA would not have approved a change" to the label. In sum, if the plaintiff can point to the existence of "newly acquired information" to support a labeling change under the CBE regulation, the burden then shifts to the manufacturer to show by "clear evidence" that the FDA would not have approved the labeling change made on the basis of this newly acquired information.

Id. at 661 (internal citations omitted). The Second Circuit later endorsed that approach in *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019). *See also McGee v. Boehringer Ingelheim Pharms., Inc.*, 2018 WL 1399237, at *4 (N.D. Ala. Mar. 20, 2018). This Court previously considered and rejected that framework. *In re Zofran (Ondansetron) Prods. Liab. Litig.*, 368 F. Supp. 3d at 114-15.

Nonetheless, this Court will continue to treat preemption as an affirmative defense, for which the manufacturer alone bears the burden of proof. To begin, the Supreme Court in *Albrecht* suggested as much:

> The underlying question for this type of *impossibility preemption defense* is whether federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law. And, of course, in order to succeed with that defense *the manufacturer must show* that the answer to the question is yes.

Albrecht, 139 S. Ct. at 1678 (emphasis added). *Albrecht* thus refers to preemption as a "defense" and states that for the defense to succeed, the manufacturer "must" make the requisite showing. *See In re Avandia*, 945 F.3d at 758 (placing the burden of proof on a defendant); *see also In re Incretin-Based Therapies Prods. Liab. Litig.*, 2021 WL 880316, at *3 (S.D. Cal. Mar. 9, 2021) (noting that preemption is an affirmative defense); *Javens v. GE Healthcare Inc.*, 2020 WL 2783581, at *4 (D. Del. May 29, 2020) (same).[26] And the First Circuit has previously treated

[26] The Second Circuit decided *Gibbons* before the Supreme Court issued its opinion in *Albrecht*. *Compare Albrecht*, 139 S. Ct. at 1672 (May 2019), *with Gibbons*, 919 F.3d at 708 (March 2019). At least three district courts in the Second Circuit have continued to apply the *Utts* framework after *Albrecht*. *See McGrath v. Bayer HealthCare Pharms. Inc.*, 393 F. Supp. 3d 161, 167 (E.D.N.Y. 2019); *Gayle v. Pfizer, Inc.*, 452 F. Supp. 3d 78, 87 (S.D.N.Y. 2020); *Ignacuinos v. Boehringer Ingelheim Pharms. Inc.*, 490 F. Supp. 3d 533, 541 (D. Conn. 2020).

impossibility preemption like any other affirmative defense. *See Celexa*, 779 F.3d at 41-43. Therefore, based on both the Supreme Court's decision in *Albrecht* and First Circuit law, the Court concludes that preemption is an affirmative defense as to which a defendant bears the burden of proof.

C. Whether GSK is Entitled to Summary Judgment

As set forth above, to prevail on a preemption defense, GSK must show that the CBE process was not available to it or that the FDA would not have approved the proposed label that plaintiffs claim was necessary. As to the latter, GSK must show that the FDA was "fully informed . . . of the justifications for the warning required by state law and that the FDA, in turn, informed the manufacturer that the FDA would not approve changing the drug's label to include that warning." *Albrecht*, 139 S. Ct. at 1678.

GSK contends that none of the four categories of information identified by plaintiffs qualify as "newly acquired information" that permitted it to use the CBE process and that none of it would have been material to the FDA during its review of the 2013 Reichmann citizen petition or the 2015 Novartis PAS. Furthermore, it contends that the FDA's rejection of the warnings proposed in the 2020 Novartis PAS was fully informed, and is clear evidence that any earlier attempt to change the label would have been rejected by the FDA.

Plaintiffs contend that GSK could have unilaterally changed its label through the CBE process after the initial label had been approved.[27] They further contend that the FDA's rejections of proposed changes to the label through the 2013 Reichmann citizen petition and the 2015 Novartis PAS application were based on incomplete evidence, because GSK had withheld

[27] As noted, Zofran was the subject of five NDAs, approved between 1991 and 1999. Plaintiffs also contend that to the extent NDA applications were pending at relevant times, GSK also had the power to change the label during the application process.

information from the agency and made material misrepresentations. According to plaintiffs, had the FDA been presented with that information, it would have required substantially stronger warnings for use during pregnancy. Finally, they contend that the FDA's recent rejection of the enhanced pregnancy warning label proposed by Novartis does not have preemptive effect, because the FDA did not consider (or reject) a proposed change concerning certain animal studies.

1. Was the CBE Process Available?

GSK first contends that none of plaintiffs' categories of information constitute "newly acquired information" as defined by the CBE process. According to GSK, none of that information reveals "risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA" that constitute "reasonable evidence of a causal association" between Zofran and a harm. (Def. Mem. at 32 (citing 21 C.F.R. §§ 201.57(c)(6)(i), 314.3)). Among other things, it contends that the researchers who performed the Japanese animal studies and the FDA itself have found that the studies do not show any evidence of such a causal association. Thus, it contends that it had no information regarding Zofran and birth defects that would have allowed it to avail itself of the CBE process and change the label to warn of that potential risk. *See McGrath*, 393 F. Supp. 3d at 170 (noting that *Albrecht* held that only "when the risks of a particular drug become *apparent*" does the manufacturer have a duty to change the warning to adequately describe the risks).

For the purposes of this motion the Court will assume, without deciding, that the information at issue constituted "newly acquired information" as defined by the CBE regulations, and that therefore GSK could have attempted to amend the Zofran label unilaterally at one or more points during the period it owned the rights to the drug. The Court will therefore evaluate whether the FDA was fully informed of the justifications for the warnings advocated for

by plaintiffs, and in turn whether the FDA informed the manufacturer that it would not approve that label change.

2. Was the FDA Fully Informed of the Justifications for the Warning?

Again, plaintiffs identify four categories of information that they contend were withheld by GSK from the FDA, which in turn led the FDA to make decisions about Zofran's label that were not fully informed. Those categories are (1) certain Japanese animal studies, (2) information concerning the biological mechanism of action, (3) certain adverse event data, and (4) information concerning GSK's involvement in the *Einarson* birth defect study. For present purposes, the principal question is whether the FDA was in possession of that information by the time of its 2021 decision on the Novartis PAS.

a. Japanese Animal Studies

GSK provided the name and study number for each of the three disputed Japanese animal studies—Nos. 100423, 100424, and 100441—to the FDA in 1993. (Jenner Decl., Ex. B at 819-20). It did not, however, provide the FDA with copies of the study reports.

As part of its 2019 citizen petition, GSK provided the FDA with full English translations of all three study reports and translated versions of the peer-reviewed Japanese publications that discussed Study Nos. 100424 and 100441. (Hill Suppl. Decl., Exs. 165-66, 169, 177-78). In connection with that petition, both GSK and plaintiffs met with representatives from the FDA CDER to discuss their views of the studies and their impact on Zofran's label. (*Id.*, Exs. 202-08).[28]

Novartis attached the English translation of the Japanese publication that discussed Study

[28] The CDER is responsible for regulating prescription drugs and is the same entity that reviewed and ultimately decided upon Novartis's 2020 PAS. (Hill Suppl. Decl., Ex. 197; GSK's April 30, 2021 Notice of FDA's Approval of Updated Labeling, Ex. A).

No. 100424 to its 2020 PAS. (*Id.*, Ex. 194).[29] Novartis also specifically referred to the animal studies in its clinical overview submitted with the labeling revisions. (*Id.*, Ex. 193 at 9).

b. Biological Mechanism of Action

GSK identified the early studies that plaintiffs contend describe the biological mechanism of action—the 1994 de Lorenzi and 2000 Kuryshev studies—in a 2005 submission to the FDA. (Hill Decl., Ex. 103 at 4460). GSK also cited the 2014 Danielsson paper on the topic in a 2015 report to the agency. (*Id.*, Ex. 95 at 4793). The FDA then discussed that 2014 Danielsson paper in its 2015 denial of the Reichmann citizen petition. (*Id.*, Ex. 32 at 10-11).

Novartis also discussed the biological mechanism of action and the 2014 Danielsson paper in the clinical overview submitted with its 2015 PAS. (*Id.*, Ex. 34 at 38).

GSK described the mechanism of action in its 2019 citizen petition and submitted the 1994 de Lorenzi study, the 2000 Kuryshev study, the 2014 Danielsson paper, and the 2018 Danielsson paper to the FDA. (Hill Suppl. Decl., Ex. 160-61). Plaintiffs submitted Dr. Danielsson's expert report, rebuttal expert report, and deposition in this case as part of its presentation to the FDA in connection with the citizen petition. (*Id.*, Ex. 208 at 1).

Finally, Novartis submitted the 2018 Danielsson paper with its 2020 PAS application and included a discussion on its findings in the clinical overview. (*Id.*, Ex. 193).

c. Adverse Event Data

GSK had a duty to make periodic disclosures to the FDA of all adverse event data it received about Zofran as part of the agency's ongoing monitoring of the drug. *See* 21 C.F.R. §§ 314.50(f)(2), 314.50(d)(5)(vi)(b), 312.23. Specifically, GSK submitted 765 Zofran-related

[29] Plaintiffs do not contend that GSK failed to provide Novartis with the disputed Japanese animal studies when Novartis took control of Zofran in 2015. (Pls. Mem. at 20).

adverse event reports and provided a detailed summary of all anomalies to the FDA in 2011. (Hill Decl., Ex. 27 at 4313-19). Novartis also submitted 1,028 Zofran-related reports from GSK's safety database to the FDA in 2015. (*Id.*, Ex. 34 at 19-36).

Plaintiffs do not contend that GSK failed to submit adverse event data to the FDA. Instead, they contend that GSK miscategorized adverse event reports in a 2005 report to the FDA and that it presented a misleading DPA to the FDA in 2015 such that an increased risk of birth defects would not have been detected.

In its 2019 citizen petition, GSK presented plaintiffs' contentions concerning adverse event reports to the FDA. (Hill Suppl. Decl., Ex. 160 at 10).

d. The *Einarson* Birth Defect Study

GSK provided the FDA with the *Einarson* study shortly after it was published in 2004. (Def. SMF ¶ 193; Hill Decl., Ex. 101). GSK also submitted a report of a birth defect that plaintiffs contend was "unreported" as an adverse event in its 2011 submissions to the FDA. (Hill Decl., Ex. 27 at 4315). The FDA discussed the study in its rejection of the Reichmann citizen petition. (*Id.*, Ex. 32 at 9). Novartis also referred to the study in its clinical overview submitted with its 2015 PAS. (*Id.*, Ex. 34 at 8).

Plaintiffs contend that GSK did not fully disclose its involvement in the funding of the Einarson study to the FDA. In its 2019 citizen petition, GSK presented plaintiffs' contentions to the FDA. (Hill Suppl. Decl., Ex. 160 at 10-11).

e. Conclusion

In summary, all of the information concerning the safety of Zofran that plaintiffs allege was withheld from the FDA had been provided to it by the time of the 2020 Novartis PAS. Based on the undisputed evidence, the FDA was "fully informed" of the justifications for the warning label that plaintiffs contend was required by state law.

3. Did the FDA Inform the Manufacturer That It Would Not Approve the Warning?

The next question is whether the FDA informed the manufacturer that it "would not approve changing the drug's label" to include the warning that plaintiffs contend is required by state law. *See Albrecht*, 139 S. Ct. at 1678.

As noted, on June 4, 2020, Novartis specifically requested warnings concerning the use of Zofran during pregnancy, based on the possibility of fetal injury. The FDA rejected that proposal, stating that "the available data do not support a recommendation to avoid Zofran in pregnancy" and that "one cannot conclude that maternal exposure to ondansetron is associated with adverse developmental outcomes." (Hill Suppl. Decl., Ex. 197 at 6486-87). Instead, on April 29, 2021, the FDA approved a label that does not include warnings concerning use during pregnancy.

The new label expressly discusses human epidemiological studies that investigated the association between Zofran and birth defects. (GSK's April 30, 2021 Notice of FDA's Approval of Updated Labeling, Ex. B at 7-8). But it states that those studies have "reported inconsistent findings and have important methodological limitations that preclude conclusions about the safety of ondansetron use in pregnancy" and "preclude an assessment of a drug-associated risk of adverse fetal outcomes." (*Id.* at 7).

As to animal studies, the approved label states that "[r]eproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered intravenously during organogenesis at approximately 3.6 and 2.9 times the maximum recommended human intravenous dose of 0.15 mg/kg given three times a day, based on body surface area, respectively." (*Id.*). The label further states that animal studies showed "no significant effects of ondansetron on the maternal animals or the development of the offspring,"

and "no effects upon the pregnant rats and the pre- and postnatal development of their offspring." (*Id.* at 8).

The FDA rejected Novartis's proposed warning that "[t]he use of ondansetron in pregnancy is not recommended," and instead added that "[a]vailable postmarketing data have not identified a drug-associated risk of miscarriage or adverse maternal outcomes" and that "[o]ndansetron exposure in utero has not been associated with overall major congenital malformations in aggregate analyses." (Hill Suppl. Decl., Ex. 197 at 6485-86). It also removed a warning that stated "[i]t is possible that ZOFRAN can cause fetal harm when used during pregnancy," and removed a section that stated "[a]dvise females of reproductive potential that it is possible that ZOFRAN can cause harm to the developing fetus." (*Id.* at 6479, 6487).

Plaintiffs here allege that at the time of their alleged injuries, Zofran should have carried a Pregnancy Category C label, "which would have informed physicians of the existence of animal data suggesting adverse fetal effects." (Pls. December 3, 2020 Suppl. Mem. at 1).

The FDA thus approved a label that contains language that is directly contrary to the language proposed by plaintiffs. And it rejected language proposed by Novartis that would have cautioned against the ingestion of Zofran during pregnancy.

Furthermore, it is undisputed that the FDA's approval of the Novartis label on April 29, 2021, constituted a final agency action "taken pursuant to the FDA's congressionally delegated authority." *Albrecht*, 139 S. Ct. at 1679. Thus, there appears to be an "irreconcilabl[e] conflict" between the requirements of federal and state law, requiring preemption of the state-law claims. *Id.*; *see also Lyons v. Boehringer Ingelheim Pharms., Inc.*, 491 F. Supp. 3d 1350, 1367 (N.D. Ga. 2020) (finding the plaintiff's claims to be preempted when "based on the same data and analyses that [the] [p]laintiff use[d] as a basis for their warning label criticisms, the FDA ha[d] twice

rejected" a proposal to warn of the risk advocated for by the plaintiff),

Plaintiffs nonetheless contend that there is insufficiently clear evidence that the FDA would have rejected a label with enhanced pregnancy warnings related to *animal studies*, as opposed to generalized safety warnings or warnings related to *human epidemiological studies*. As noted, the current label states that animal studies have not shown any fetal risk during pregnancy. Novartis did not propose any changes to that language in its 2020 PAS. (Hill Suppl. Decl., Ex. 192 at 7534-35). According to plaintiffs, because Novartis did not propose such a change, the FDA necessarily did not consider changing the warning as to animal studies; and not having considered it, the FDA cannot be said to have rejected it.

As an initial matter, 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, or that Novartis did not inform it of the relevant data. According to the undisputed evidence, the FDA was asked to do so on multiple occasions. In its letter accompanying the PAS, Novartis specifically referred to GSK's 2019 citizen petition and "acknowledge[d] GSK's request that [the] FDA review the four categories of information discussed within the Citizen Petition and take actions as the [FDA] deems appropriate." (*Id.*, Ex. 190 at 1-2). Those four categories included the Japanese animal studies on which plaintiffs rely. In its clinical overview submitted with its proposed revisions, Novartis also described Dr. Danielsson's 2018 paper that included his proposed biological mechanism of action and referred to the disputed Japanese animal studies. (*Id.*, Ex. 193 at 9). The FDA even met with plaintiffs' counsel to discuss the potential impact of those studies, and it had been provided with copies of plaintiffs' expert reports from this litigation. The FDA was thus pointed specifically to the very evidence that plaintiffs contend requires a label warning that animal studies showed Zofran had adverse effects on fetal development.

Again, plaintiffs contend that none of that is significant, because Novartis "did not suggest that the animal study section of the labeling was inaccurate in any respect." (Pls. December 3, 2020 Suppl. Mem. at 4-5). But that assumes that the FDA was not following the statutory requirement that it consider "all" relevant information in evaluating the PAS. *See* 21 U.S.C. § 201.57(c)(9)(i)(B). In this context, at least, the Court will not assume that the FDA failed to perform, in fact blatantly ignored, its statutory duties to review and monitor the drug for human safety. *See In re Incretin-Based Therapies Prods. Liab. Litig.*, 2021 WL 880316, at *17 ("[T]he Court cannot simply ignore the FDA's demonstrated commitment to actively and continuously monitoring the [drug]."). [30] Accepting plaintiffs' argument would suggest that the FDA conducted a narrow and myopic review of the safety of the drug, considering only what Novartis expressly asked it to consider, and that it turned a blind eye to evidence that Zofran causes birth defects. That is highly unlikely, to say the least. And it is also unlikely that the FDA intended to leave open the possibility that enhanced pregnancy warnings would be appropriate in a different section of the label—and that it refused to take up the issue with Novartis based on the technical point that Novartis had not sought to change that specific section. [31]

[30] The FDA specifically stated in its denial of GSK's citizen petition that it continued to "monitor and review available safety information related to" Zofran and that it would "take further action" if it deemed it "appropriate." (Notice by Plaintiffs' Lead Counsel of FDA Denial of GSK's Citizen Petition, January 15, 2021, Ex. A at 16).

[31] It is also worth noting what the FDA has itself said about its role in drug labeling in this very matter. In its denial of GSK's 2019 citizen petition, the FDA detailed its "approach to the review of [safety-related] information in the context of relevant statutory and regulatory requirements." (Notice by Plaintiffs' Lead Counsel of FDA Denial of GSK's Citizen Petition, January 15, 2021, Ex. A at 2). It specifically stated that it "evaluates whether safety-related labeling changes are warranted based on the review of *all* relevant information available to the Agency," and that the FDA "may recommend substantive revisions to data and information described in draft labeling based on the Agency's evaluation and analysis of data submitted in the application . . . *or otherwise available to* the Agency." (*Id.* at 2-3) (second emphasis added). It also noted that the "Risk Summary [section] must contain risk statement(s) that describe for the drug the risk of adverse development outcomes based on *all* relevant human data, animal data, and/or the drugs' pharmacology." (*Id.* at 7) (emphasis added). Specifically as to Zofran, the FDA noted that it "continues to conduct risk-based postmarketing surveillance consistent with the

Plaintiffs' view is also unsupported by the case law. Multiple courts have found preemption where the manufacturer had not requested the precise warning sought by the plaintiffs when the FDA had nonetheless made it clear that it would not accept that label change. *See, e.g.*, *Cerveny*, 783 F. App'x at 808 n.9; *Thomas v. Bracco Diagnostics Inc.*, 2020 WL 1016273, at *10 (W.D. La. Feb. 27, 2020) (finding the fact that the FDA approved a label "specifically stating facts contrary to the warning sought by" the plaintiff as clear evidence that the FDA would not have approved the label change advocated for by the plaintiff); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 2021 WL 880316, at *16 (finding the second prong of *Albrecht* to be satisfied when all of the information justifying the proposed warning had been given to the FDA and the FDA approved labeling changes that did not include the proposed warning); *Ridings v. Maurice*, 444 F. Supp. 3d 973, 998 (W.D. Mo. 2020) (finding the second prong of *Albrecht* to be satisfied when all of the information justifying the proposed warning had been given to the FDA and the FDA did not revise the label to add the warning); *see also Albrecht*, 139 S. Ct. at 1679 (noting that the question of the "disapproval method" was not before it).

In short, there is "clear evidence" that the FDA would not approve changing the Zofran label to include the warning that plaintiffs contend is required by state law. The 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. Finally, in 2021, after having considered

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standards and practices" described in its response, that it has "continued to review safety-related data regarding ondansetron," and that it "will continue to monitor and review available safety information related to ondansetron products throughout the product life cycles and will take further action if [it] determine[s] it is appropriate to do so." (*Id.* at 14, 16). The FDA thus stated that it takes into account all safety information: it did not say that it only investigates the evidence that was directly referenced in a proposed label change when evaluating the appropriate label for a drug. *See Cerveny*, 855 F.3d at 1103 ("[A] factual dispute cannot be based on speculation that the FDA would jettison its legal requirements . . . .").

the very evidence that plaintiffs contend requires an enhanced warning—indeed, after reviewing plaintiffs' evidence and plaintiffs' expert witness reports—the FDA did so again. Preemption does not require a fourth attempt. *See Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 814-15 (7th Cir. 2018) ("The preemption analysis asks only whether GSK could have added the adult-suicidality warning through the CBE regulation, . . . not whether GSK could have persuaded the FDA after already asking four times to include that warning and being told no four times."); *Lyons*, 491 F. Supp. 3d at 1367 ("The FDA's repeated refusal to allow [d]efendant to warn that P-gp inhibitor co-medication is a risk factor for bleeding constitutes clear evidence that the FDA would have rejected the warning the [p]laintiff seeks."). Again, there can be little doubt that the FDA would not approve the label that plaintiffs say is required by state law.

4. Should the Analysis Be Different Because Novartis, Not GSK, Requested the Label Change?

The final question is whether the analysis should be different because Novartis, not GSK, was the party that requested the label change and to which the FDA rejection was directed.

The essential question in the preemption analysis is whether a manufacturer would be permitted to add a warning proposed by a plaintiff to a drug's label. *Bartlett*, 570 U.S. at 480. The Supreme Court has held that the focus of that inquiry is on the FDA: whether the *agency* was fully informed of the reasons underlying the proposed warning and whether the *agency* made it clear that it would not have approved a label that included that warning. *See Albrecht*, 139 S. Ct. at 1679 ("We do note, however, that the only *agency actions that can determine the answer to the preemption question*, of course, are agency actions taken pursuant to the FDA's congressionally delegated authority.") (emphasis added).

Preemption thus does not depend on whether the defendant manufacturer is the one who asked for the changes, or to which the FDA explicitly communicated its decision. For example,

plaintiffs here do not contend that the FDA review process changed when Novartis bought Zofran from GSK. Nor do they allege that the drug itself changed at any point after the sale. Because nothing material changed, the preemptive effect of the FDA's rejection of Novartis's proposed changes remains the same.

Indeed, if GSK had never sold Zofran to Novartis, and itself submitted the 2020 PAS, it would be clear that plaintiffs' claims would be preempted based on the FDA's response to that PAS. Similarly, if Novartis had owned Zofran for the entirety of the relevant period, the FDA's rejection of its 2020 PAS would clearly preempt claims against Novartis from patients who took Zofran during the time period that plaintiffs in this lawsuit did. The fact that the identity of the manufacturer changed is not a material event for preemption purposes.

In *Cerveny*, the Tenth Circuit found that the plaintiffs' claims were preempted because the FDA had rejected a citizen petition that advocated for the same warning that the plaintiffs asserted. 855 F.3d at 1105;[32] *see also In re Incretin-Based Therapies Prods. Liab. Litig.*, 2021 WL 880316, at *16 (finding preemption based, in part, on the FDA's denial of a citizen petition); *Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1274 (W.D. Okla. 2011) (noting that the FDA rejected a citizen petition advocating for warnings for Prozac, a different drug within the same category of drugs as Effexor, as part of finding that the plaintiff's claim for the same warnings in Effexor were preempted). There is no obvious reason why an FDA rejection of a citizen petition should have preemptive effect, but an FDA rejection of a PAS from a successor manufacturer should not. The Supreme Court itself in *Albrecht* implied that the FDA could "inform[] the drug manufacturer that the FDA would not approve changing the drug's label to include that warning"

[32] The Tenth Circuit did not find that *Albrecht* changed that analysis. *Cerveny*, 783 F. App'x at 808 n.9 (noting that it saw "nothing in *Wyeth* or *Albrecht* excluding Aventis from justifying preemption on" the basis of the FDA rejecting a citizen petition).

without responding to a specific request from that manufacturer. *Albrecht*, 139 S. Ct. at 1678. In listing the "agency actions that can determine the answer to the preemption question" the court listed not only formally rejecting a warning label, which can only be proposed by the current drug manufacturer, but rather also listed any actions "carrying the force of law." *Id.* at 1679.

Furthermore, it would be arbitrary to treat two manufacturers differently by allowing one to assert preemption as a defense to a failure-to-warn claim when the FDA has rejected a plaintiff's proposed warning, and to not allow the other. No apparent rational policy goal would be served by making that distinction. The significance of the FDA's response to plaintiffs' proposed warning is exactly the same when it responded to a PAS submitted by Novartis as it would have been if GSK still owned Zofran and thus the FDA responded to a PAS submitted by GSK.

Finally, the fact that the FDA did not approve the warning in 2021 is clear evidence that it would not have approved of the warning at any earlier time. Plaintiffs have not identified any cases where a court has found that state-law claims were preempted only *prospectively* from the time of the court's opinion. To the contrary, courts have found when the FDA communicates that it would not approve a label change that the claims of plaintiffs who were injured before that FDA action are preempted. *See, e.g.*, *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010) (finding a plaintiff's claim for an injury that occurred before the FDA's rejection of a proposed label change, which was clear evidence that it would not have accepted the plaintiff's proposed warning, to be preempted); *Rheinfrank v. Abbot Lab'ys, Inc.*, 680 F. App'x 369, 386 (6th Cir. 2017) (finding the FDA's rejection of a plaintiff's proposed warnings in 2008 to be clear evidence that it would have rejected the warning in 2003 and noting that "as of 2008 the FDA did not believe the state of the data supported a developmental delay warning,

[and so] it stands to reason that as of 2003, with even less data to go on, the FDA would similarly have rejected a developmental delay warning"); *Willis v. Abbot Lab'ys, Inc.*, 2021 WL 5988215, at *4 (W.D. Ky. Dec. 1, 2017) (same); *In re Depakote*, 87 F. Supp. 3d 916, 922 (S.D. Ill. 2015) (finding the FDA's rejection of a plaintiff's proposed warning in 2006 to be clear evidence that it would have rejected that warning in 1999); *Dobbs*, 797 F. Supp. 2d at 1277 (holding that the FDA's finding that there was no evidence to support the warning advocated for by the plaintiff in 2007 was clear evidence that the FDA would have rejected that warning in 2002).

In its first *Cerveny* opinion, the Tenth Circuit noted the importance of the timeline in the preemption analysis. In that case, the plaintiff took the drug in 1992 and the FDA rejected a citizen petition proposing the same warnings for which the plaintiff advocated in 2009. *Cerveny*, 855 F.3d at 1105. In its opinion, the court distinguished its facts from that of *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387 (7th Cir. 2010), in which the FDA rejected a citizen petition *before* the plaintiff's injury and thus the Seventh Circuit found that, due to the potential for new data to have emerged between the FDA's action and the plaintiff's injury, the rejection of the citizen petition could not constitute clear evidence that the FDA would have rejected the warning at the time of the plaintiff's injury. *Id.* at 395; *see also Dolin*, 901 F.3d at 815 (noting that the FDA's rejection of a warning at one point in time does not definitively answer whether claims of plaintiffs who were injured *after* that time are preempted and that in that scenario, courts must decide whether a manufacturer had newly acquired information between the time of the FDA's rejection and the plaintiff's injury that would have allowed it to change the label through the CBE process). Noting the difference in the "temporal gap" between its facts and those present in *Mason*, and the lack of the possibility of new facts having emerged between the FDA action and the plaintiff's injury in its case, the *Cerveny* court found that the 2009 rejection

of the citizen petition constituted clear evidence that the FDA would not have approved of the plaintiff's desired warning in 1992. *Cerveny*, 855 F.3d at 1103. Thus, the FDA's 2021 approval of a Zofran label with language contradictory to the warning advocated for by plaintiffs constitutes clear evidence that the FDA would have rejected plaintiffs' proposed label at the earlier time of plaintiffs' injuries.

To permit lawsuits to proceed against GSK today—when such cases could not proceed against Novartis for the very same drug, bearing the very same warning labels, to recover for the very same alleged injuries—would not appear to further any valid policy interest. Again, this is not a situation where a state may elect to provide greater protection to its residents than the federal government would provide; the FDA does not simply provide a minimum level of warning that may be exceeded by manufacturers in order to satisfy state law. A result that would permit lawsuits to proceed against GSK, but not Novartis, would not protect consumers, deter drug manufacturers from bringing unsafe products to market, or protect the role of the states in a federal form of government. Instead, it would simply provide a windfall to a small group of plaintiffs, and might well discourage physicians from prescribing a useful pharmaceutical product that the FDA has concluded is reasonably safe. In short, a finding that lawsuits against Novartis are preempted, but those against GSK are not, would be an exercise in the most empty type of formalism.

D. Conclusion

In summary, based on the evidence in the record, GSK has met its burden of proving a preemption defense. Plaintiffs contend that the Zofran label should have included an enhanced birth-defect warning that ingesting the drug during pregnancy may have an adverse effect on the fetus. The FDA was fully informed of the justifications for such a warning and the FDA, in turn, informed the manufacturer of Zofran that it would not approve a change to the drug's label to

include such a warning when it formally approved the new Zofran label in April 2021. Plaintiffs' claims—all of which, in substance, are premised on a failure to warn—are therefore preempted by federal law.

V. Conclusion

For the foregoing reasons, defendant's renewed motion for summary judgment based on federal preemption is GRANTED. This memorandum and order shall apply to all cases presently pending in this multi-district litigation proceeding.

So Ordered.

/s/ F. Dennis Saylor IV
F. Dennis Saylor IV
Chief Judge, United States District Court

Dated: June 1, 2021