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. <u>Warning Labels for Pregnancy</u>

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. The Approval of the Zofran Label

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. <u>Adverse Event Data</u>

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

[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