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 MOTION FOR SUMMARY JUDGMENT BASED ON FEDERAL PREEMPTION

SAYLOR, 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 moved 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. For the following reasons, the motion will be denied.

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 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.

At some point, the FDA became aware that Zofran was being prescribed to pregnant women in significant numbers. In 2010, the FDA requested that the 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 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 short, whether Zofran poses a risk to fetal safety has been considered, and rejected, by the FDA on multiple occasions since the drug's initial approval. Even 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 "[a]vailable data do not reliably inform the association of Zofran and adverse fetal outcomes."

Plaintiffs nonetheless contend that ingestion of Zofran during pregnancy in fact causes birth defects, that the label should contain such a warning, and that GSK's failure to provide such a warning should result in tort liability under state law. Plaintiffs contend that the FDA's initial approval of Zofran in 1991, and its subsequent rejection of label changes, were based on incomplete information—essentially, because GSK withheld certain data from the FDA and made material misrepresentations. GSK denies that it withheld information and contends that any state-law failure-to-warn claims are preempted by federal law.

The potential 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.

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 its safety, subject to later FDA approval. Because of the existence of the CBE process, the Supreme Court has held that a drug company can in fact add safety information to its label without FDA approval. *See Wyeth v. Levine*, 555 U.S. 555, 570-71 (2009). As a result, a drug company may prove that federal law preempts state law only if it can show by "clear evidence" that the FDA would have rejected the warning that plaintiffs contend state law required. *Id.* at 571.

Here, there is little doubt that the FDA *would have* rejected plaintiffs' proposed warning: it in fact *did* reject it, at least in substance. But plaintiffs contend that GSK's failure to make complete disclosures to the FDA means that the agency's decisions were not fully informed, and therefore a finding of federal preemption is precluded.

The legal framework for considering preemption claims is muddy at best. Among other things, there is considerable debate as to such basic matters as the required standard of proof and the appropriate roles of the judge and jury. The United States Supreme Court recently granted a writ of certiorari in an FDA preemption case, presumably to clarify some of those issues. *See In re Fosamax*, 852 F.3d 268 (3d Cir. 2017), *cert. granted sub nom. Merck Sharp & Dohme Corp. v. Albrecht*, 138 S. Ct. 2705 (2018).

In the meantime, this Court is required to consider the matter under the existing

framework, without the benefit of that guidance, and notwithstanding the fact that the applicable principles as determined by this Court may eventually prove to be erroneous. Under the existing legal framework, as this Court understands and interprets it, the basic factual question underlying preemption—that is, whether the FDA would have rejected the label had it been presented with the evidence plaintiffs contend was withheld—must be resolved by a jury.

Accordingly, and for the following reasons, the motion of GSK for summary judgment based on preemption will be denied.

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)(F); 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 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." *Mutual 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 565.

2. The Process for Changing Labels

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); 21 C.F.R. § 314.93. 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 Practices 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), 314.70(b)(2). 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).

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 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, 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, Inc. v. Mensing*, 564 U.S. 604, 611 (2011) ("It is undisputed that Minnesota and Louisiana tort law require a drug manufacturer that is or should be aware of its product's danger to label that product in a way that renders it reasonably safe."); *Wooderson v. Ortho Pharm. Corp.*, 681 P.2d 1038, 1049 (Kan. 1984) ("It is well settled, however, that the manufacturer of ethical drugs bears the additional duty of making timely and adequate warnings

to the medical profession of any dangerous side effects produced by its drugs of which it knows, or has reason to know.") (collecting cases from various jurisdictions).

4. Warning Labels for Pregnancy

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

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

21 C.F.R. § 201.57(c)(9)(i)(A)(2).

That classification system was eliminated by the FDA when it issued a final rule amending the regulations concerning pregnancy and lactation labeling. 79 Fed. Reg. 72064 (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. 10).

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. 3).[1] The 1991 approval was for an injection

[1] A predecessor of GSK, Glaxo, Inc., sponsored the original new drug application for Zofran. (Master

formulation; in 1992, 1995, 1997, and 1999, the FDA approved four additional formulations, covering oral tablets, premixed injections, oral solutions, and orally disintegrated tablets, respectively. (*Id.* Exs. 3, 6-9).

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. 17 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 Labs., Inc.*, 723 F. Supp. 2d 395, 397 n.2, 398-99 (D. Mass. 2010); *see also Buckman Co. v Plaintiffs' Legal Committee*, 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. (Hill Decl. Ex. 3). Between 1992 and 2016, the "Use in Specific Populations" section of the approved label for intravenous Zofran containing the pregnancy category B designation

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Compl. ¶ 4).

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 4; *see also* Exs. 3, 7, 28).

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. 12). 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 has included a summary of that analysis in this submission." (*Id.* Ex. 14). 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. 15).

E. The 2013 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. 16).[2] 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 OB/GYNs 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. 17 at 1). His petition contended that Zofran "may lead to adverse maternal and fetal events or outcomes" if ingested during pregnancy. (*Id.*).[3]

On October 27, 2015, the FDA denied the petition. (*Id.* Ex. 17). 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 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:

[2] A citizen petition is a request that FDA "issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action." 21 C.F.R. § 10.30(b)(3). 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").

[3] Reichmann supplemented his petition five times. (*Id.*).

> 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. 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 Zofran from GSK in 2015. On September 22, 2015, Novartis submitted to the FDA a proposed update to the Zofran pregnancy labelling along with a clinical overview. (*Id.* Ex. 21).[4] The proposal included several changes to the "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:

  > "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).

[4] 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. (*Id.* Ex. 21).

- 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).

(*Id.* Exs. 21, 22).

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. 22).

In the conclusion section of the 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. 23 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 advents 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. 24 at 2610). 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 2611). 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 2604).

The FDA responded in April 2015, again rejecting proposed language that the "use of ondansetron in pregnancy is not recommended." (*Id.* Exs. 23, 25, 27-28). The FDA stated that a "limitations on use" statement is "not intended to prohibit off-label use." (*Id.* Ex. 25 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, in September 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. 23 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. 25 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 the evidence to show that Zofran is ineffective when used for nausea and vomiting in pregnancy . . . . There is also no preponderance of the evidence that the benefits [of Zofran] do not generally outweigh its risks." (*Id.* Ex. 27 at 4445).

- "[W]e do not believe that there is any basis to suspect drug attribution to [reported] congenital malformation 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 states the following, among other things:

- "Available data do not reliably inform the association of Zofran and adverse fetal outcomes" (*Id.* at 4451);

- "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 4452); and

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

G. 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 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, Glaxo Nippon. (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).

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. (Jenner Decl. Ex. A (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 contends that Study No. 100423 "was merely a preliminary dose-range

finding completed in advance of the definitive study, No. 100424," and 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. 32, NTX/88/005 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 historic 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. (Jenner Decl. Ex. A (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 abnormalities 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 observed to have no teratogenicity.

(Hill Decl. Ex. 34, NTX/99/001 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 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." (Jenner Decl. Ex. A (Danielsson Report) at 56). It further contends that the study investigators concluded that "[t]he effects of [Zofran] were not

observed in the incidences of external, visceral or skeletal anomalies and variations in fetuses, and there were no findings indicating the teratogenicity of [Zofran]." (Hill Decl. Ex. 33, NTX/99/000 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. The publication had English-language tables, data provided in Arabic-numeral format, and (for six of the seven) English-language abstracts. Two of the three studies at issue were among that group. (Hill Decl. Exs. 37-38).

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, provided the name and study number for each of the three studies, among other reproduction studies conducted on Zofran in Japan. 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.*). GSK did not provide the FDA with copies of the studies themselves, which were only available in Japanese at that time. (Def. Resp. ¶¶ 4-6).

In a September 11, 1997 pharmacology review, the FDA, having reviewed Study No. 100424, 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. 40 at 191).

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 production studies as requested." (Jenner Decl. 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 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. 17 at 12). The denial specifically cited a summary of data written in 1989 by Dr. Tucker, a GSK employee. (Jenner Decl. Ex. O at 751). The summary did not include a discussion of Japanese animal studies. (*Id.*). 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. (Hill Decl. Ex. 17 at 7-12).[5]

[5] 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. 17 at 18 n.56).

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 Rebar Dep. Ex. 42 at 313)

The results of the Japanese animal studies were not otherwise provided to the FDA by GSK or Novartis.

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. ¶¶ 7, 16, 19-21, 30-31, 34-36, 39-40). The disputed mechanism of action is alleged to cause fetal heart defects when Zofran "inhibits hERG potassium channels" and disrupts cardiac rhythm. (Pls. CMF ¶¶ 11-19).

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. 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.

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). The study reported that Zofran inhibits hERG potassium channels, which is the mechanism of action by which Zofran

can cause QT prolongation—a condition that plaintiffs characterize as a serious disturbance of the heart's rhythm. (*Id.*). Other than the characterization of QT prolongation as a "serious" disturbance of the heart's rhythm, GSK does not directly dispute those findings. It contends, however, that the study 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).

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). That study similarly reported that Zofran was associated with QT prolongation due to its inhibition of hERG potassium channels. (*Id.*). GSK again does not directly dispute that finding, but nonetheless contends the study was not designed to examine the effect of Zofran on QT prolongation in humans. (Def. Resp. ¶ 12).[6]

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 and death." (Jenner Decl. Ex. U at 669, 707). The document cited a 1994 paper co-authored by Dr. Danielsson. 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

[6] 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 010). 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 repolarization." (*Id.*). However, the director went on to note that "the evidence [GSK had] that ondansetron causes QT prolongation (a measure of cardiac repolarization) is not very convincing," and that "the clinical relevance of the non-clinical finding referred to [by the Kuryshev study] is uncertain." (*Id.* at 013).

in 2002. (Pls. CMF ¶ 16; Jenner Decl. Ex. A (Danielsson Report) at 4).[7]

GSK, however, contends that "[t]he mechanism discussed [in the document] does not refer to ondansetron or 5-HT3 receptor antagonists." It contends that it "never determined that Zofran could cause birth defects of any kind by the mechanism discussed" in the document, and that "no drug-induced embryolethality or teratogenicity was observed in the Zofran animal studies." (Def. Resp. ¶ 16). Finally, it contends that Dr. Danielsson's mechanism is merely hypothetical, and that his opinions are not reliable, adequately supported, or admissible. (*Id.* ¶ 18).

In its September 2015 submission to the FDA, Novartis's clinical overview described, among other sources, two papers authored by Dr. Danielsson in 2007 and 2014. It characterized the 2014 paper as having found that "hERG channel blockade could induce developmental toxicity generally due to embryonic heart arrhythmias leading to transient hypoxia and reperfusion injuries." (Jenner Decl. Ex. J at 307). 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. 27 at 451).

3. Adverse Event Data

Plaintiffs also allege that beginning in 2005, GSK failed to disclose, or incorrectly coded,

[7] 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).

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.").[8]

GSK coded adverse events involving Zofran using the Medical Dictionary for Naming

[8] 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).

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).

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 at 511). 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 129, 165). Plaintiffs allege this "limited analysis necessarily undercount[ed] the reporting of congenital cardiac adverse events which 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 19).

GSK has responded to that claim in a number of ways. First, it denies that the adverse events 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. 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 given the background incidence rate of heart defects. (Hill Decl. Ex. 27 at 450, 465).

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 20). 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 4, 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 opinions of top GSK scientists that the study it helped bring to light was incredibly flawed and insufficiently powered." (*Id.*, citing Jenner Decl. Exs. G at 661, 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 11-12; Def. Resp. ¶¶ 33, 35, citing Jenner Decl. Ex. I at 913-14).

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. General 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 fact finder 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. National 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." *American Steel Erectors, Inc. v. Local 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." *United States v. Arizona*, 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 labelling 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, n.8 (2011). Although the *PLIVA* court held that federal law preempted the 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 Practices 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." *Id.*

The application of the *Wyeth* preemption standard has proved challenging, to say the least. As the Third Circuit has observed, "[the] standard is cryptic and open-ended, and lower courts have struggled to make it readily administrable." *In re Fosamax*, 852 F.3d 268, 282 (3d

Cir. 2017). Indeed, basic questions about the application of the standard—such as whether "clear evidence" refers to the applicable standard of proof, and whether the ultimate question is one of fact for the jury—do not have clear answers. *Id.* The First Circuit has addressed FDA preemption under *Wyeth* on two occasions, without addressing the more difficult issues raised by the opinion.

In *Gustavsen v. Alcon Laboratories, Inc.*, 903 F.3d 1, 9-14 (2018), the court did not reach the "clear evidence" question, because it held that as a threshold matter, the change to the drug product that the plaintiffs sought was a "major" change under FDA regulations. Because FDA approval is required before a manufacturer can make "major" changes to a drug product, the court held, the "plaintiffs' attempt to use state law to require such a change is preempted." *Id.* at 14 (citing *PLIVA*, 564 U.S. at 620).

In *Celexa*, 779 F.3d at 41-43, the court again did not reach the "clear evidence" question, because the plaintiffs could not point to any "newly acquired information" that the defendant could have used to change its label through the CBE process. Accordingly, the defendant could not independently change its label in the manner plaintiffs sought, and therefore their claims were preempted. *Id.* at 43 (citing *PLIVA*, 564 U.S. at 624).

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 plaintiffs contend should have been made. There are, however, multiple unresolved questions concerning the analytic framework for resolving questions of FDA preemption.

B. Whether Preemption is an Affirmative Defense

The first question is whether preemption is an affirmative defense, as to which the manufacturer bears the burden of proof. It appears that the answer to that question is yes. *See In re Fosamax*, 852 F.3d at 271, 295; *see also Wyeth*, 555 U.S. at 573 ("[i]mpossibility pre-emption is a demanding defense").

Nonetheless, and as with many other issues in this case, the answer is not necessarily straightforward. In *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644 (S.D.N.Y. 2017), the District Court concluded that "[p]ost-FDA approval preemption analysis proceeds in two stages." 251 F. Supp. 3d at 661.

> 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 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. (citations omitted).[9]

That analytical framework has some superficial appeal, but raises a number of potential issues. First, that burden-shifting framework does not appear to have been adopted by any appellate court. While district courts are frequently called upon to break new ground in dealing with legal issues, it is far from clear that this is an appropriate circumstance in which to do so. Perhaps more importantly, the *Utts* framework seems to suggest that a plaintiff in a failure-to-

[9] A similar approach was adopted by the court in *McGee v. Boehringer Ingelheim Pharmaceuticals, Inc.*, 2018 WL 1399237, at *4 (N.D. Ala. Mar. 20, 2018).

warn case against a brand-name manufacturer *must* establish, as a part of its affirmative case, that there was "newly acquired information" sufficient to support a labeling change under the CBE process. Does that mean all plaintiffs in such failure-to-warn cases must always assume that the manufacturer will raise an FDA preemption defense, and allege and prove facts sufficient to rebut it? Or is that requirement triggered only if a manufacturer raises preemption as a defense? If the latter, does that mean the burden shifts multiple times: it begins with the manufacturer (to point to facts sufficient to raise a preemption defense), then shifts back to the plaintiff (to point to "newly acquired information" sufficient to show that the CBE process could be used), then back again to the manufacturer (to show by "clear evidence" that the FDA would not have approved the change)? That framework seems unduly cumbersome and unnecessary, and appears to run counter to First Circuit law.

In *Celexa*, the First Circuit observed that "a necessary step in defeating [the manufacturer's] preemption defense is to establish that the complaint alleges a labeling deficiency that [the manufacturer] could have corrected using the CBE regulation." 779 F.3d at 41. The court then stated that the complaint in that case plainly alleged that the defendant was a brand-name manufacturer and the drug was a brand-name drug (and, therefore, the manufacturer could use the CBE process). *Id.* It then went on to state: "So the question to which we now turn is whether the CBE regulation allows a brand name manufacturer to make the particular type of change that plaintiffs say [the manufacturer] needed to have made to avoid liability under [state] law." *Id.* After reviewing the allegations of the complaint, the court concluded that it did not, because the complaint could not plausibly be read as relying on newly acquired information. *Id.* at 42-43.

The *Celexa* court thus did not employ a burden-shifting framework; rather, it treated

preemption like any other affirmative defense. When an affirmative defense is raised, the burden does not shift to the plaintiff to disprove it. Nonetheless, a defendant can prevail on a motion to dismiss (if the allegations of the complaint are insufficient) or on summary judgment (if the undisputed evidence is insufficient). But the burden never shifts from the defendant.[10]

Under the circumstances, and again without benefit of guidance from a higher court, it appears that FDA preemption is an affirmative defense, like any other, and that a burden-shifting framework is inappropriate. A manufacturer may prove that the CBE process was not available to implement changes unilaterally (because, for example, there was no "newly acquired information") *or* that the FDA would not have approved the proposed label change. It can do so by pointing to shortcomings in the complaint (on a motion to dismiss) or the evidence (on a motion for summary judgment). In short, and in keeping with what seems to be the intent of the court in *Wyeth*, the Court concludes that preemption is an affirmative defense as to which defendant bears the burden of proof.

C. Whether Preemption Presents a Question of Fact for the Jury

The next question is whether the preemption issue is a question of law, to be resolved by the judge, or a question of fact, to be resolved by the jury.

In *United States v. Rhode Island Insurers' Insolvency Fund*, 80 F.3d 616 (1st Cir. 1996), the First Circuit stated that "a federal preemption ruling presents a pure question of law subject to plenary review." *Id.* at 619 (citing *New Hampshire Motor Transp. Ass'n v. Town of Plaistow*, 67 F.3d 326, 329 (1st Cir. 1995)). In that case, the issue was whether the federal Medicare

[10] Consider, for example, the statute of limitations, which is a form of affirmative defense. If a complaint in a personal injury case alleges facts suggesting that the claim did not accrue within the limitations period, a defendant may move to dismiss the complaint as untimely. If the complaint satisfies the plausibility standard, the defendant may later move for summary judgment on the same ground. The plaintiff may defeat summary judgment by producing evidence sufficient to show a genuine issue of material fact as to timeliness (for example, that accrual of the action should be delayed by the discovery rule).

Secondary-Payer Act, 42 U.S.C. § 1395y(b)(2)(A), preempted various sections of the Rhode Island Insurers' Insolvency Fund Act. *Id.* at 617. There were no factual issues in dispute, and the district court had granted judgment on the pleadings for the United States. *Id.* at 618-19.

In theory, that broad language ought to resolve the issue. The problem, though, is that this dispute does not involve a simple matter of comparing the text of two statutes: it involves complex matters of science interacting with a complex regulatory environment, and it very much involves disputed issues of fact. The preemption question thus cannot be resolved without taking evidence—again, the *Wyeth* opinion uses the phrase "clear *evidence*"—and making factual findings. Again, without guidance from a higher court, it is entirely unclear how this Court should go about making such factual findings. In particular, it is unclear whether the Court should conduct an evidentiary hearing (in this case, what amounts to a lengthy bench trial) to resolve factual disputes.

In *Fosamax*, the Third Circuit concluded that proof by "clear evidence" involved a question of fact, not law. 852 F.3d at 286. In substance, the court found that the inquiry involves (1) assessing the probabilities of future events, (2) weighing conflicting evidence and drawing inferences from facts, and (3) assessing motives and thought processes, all tasks traditionally reserved for the jury. *Id.* at 289-91. As to the third point, the court noted:

> [T]he task of predicting the FDA's likely actions requires multiple assessments of FDA officials' motives and thought processes . . . . These are all, essentially, inquiries about motive or state of mind: what were FDA officials thinking, and how would that disposition have conditioned their response to plaintiffs' hypothetical proposed warning? And questions of motive, intent, and state of mind are typically understood to be fact questions committed to the jury rather than the court.

852 F.3d at 290-91.

Although it did not address the issue directly, the Ninth Circuit seemed to take a similar

position when it reversed a district court's summary judgment order on preemption that had found that "new safety information" about the drug in question was irrelevant. The court concluded that "[u]ncertainty about whether the FDA considered the 'new safety information' and whether it would have altered the FDA's conclusion establishes that a *disputed issue of material fact* should have prevented entry of summary judgment on the defendants' preemption claim." *In re Incretin-Based Therapies Prods. Liab. Litig.*, 721 Fed. Appx. 580, 584 (9th Cir. 2017) (emphasis added). If preemption were solely a question of law, it presumably would have been unnecessary to resolve a disputed issue of material fact.

Other circuits have declined to resolve the issue, finding defendants entitled to judgment as a matter of law based on the undisputed facts. *See Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 812-13 (7th Cir. 2018) (concluding that it was not necessary to determine whether "clear evidence" involves a factual or legal question because "given the facts [of the] case, no reasonable jury could find that the FDA would have approved [plaintiffs' proposed warning] under the CBE regulation"); *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1099, 1103 n.11 (10th Cir. 2017) (assuming for the sake of argument that "clear evidence" is a question of fact but finding the conclusion would remain the same if it were a question of law, given the undisputed facts "would foreclose any reasonable juror from finding that the FDA would have approved [plaintiffs' proposed] warnings").

At least one court has explicitly decided that *Fosamax* is wrongly decided, and that FDA preemption is a question of law. In *In re Risperdal and Invega Product Liability Cases*, 2017 WL 4479317 (Cal. Super. July 24, 2017), the court observed:

> Plaintiffs have not established that the determination of whether or not federal preemption applie[s] is a jury question. This Court does not see this as a close question but as the only correct ruling that could be made here. . . . [T]here is no role for a jury in resolving the question of federal preemption in these cases—that

> is, whether or not one must resolve one or more disputed antecedent factual questions to make such a ruling. Both the questions of whether proposed label changes are based on "newly acquired information" and whether there is "clear evidence" FDA would have not approved the proposed label changes are legal questions for the Court to decide.

Id. at *3. Among other things, the court observed (citing *Utts*) that matters of federal supremacy should be resolved as early as possible in a case, "which is only possible when the issue is properly considered a 'question of law' for judicial resolution without a jury." *Id.* And it also noted the practical problem of attempting to explain federal preemption to a jury. *Id.* at *2.

Those concerns are clearly legitimate. Nonetheless, the normal rule is that factual disputes are resolved by a jury, and it is doubtful, to say the least, that this Court has the authority to conclude otherwise simply because the issues are highly complex or involve important regulatory questions.

In the absence of appellate guidance to the contrary, the Court therefore concludes that the analysis of the Third Circuit in *Fosamax* is probably correct: as a general matter, the questions of whether there was "newly acquired information," and whether the FDA would have rejected plaintiff's proposed label change, are factual questions for the jury to resolve. And as with any other factual issues, those questions could be resolved, in appropriate circumstances, on a motion to dismiss or by summary judgement. Whether that is the most sensible or fair method for resolving such issues—that is, having lay jurors decide difficult issues of science and pharmaceutical regulation—is a question for Congress or a higher court to decide.

D. Whether the Term "Clear Evidence" Establishes a Standard of Proof

The next question in analyzing the preemption issue is the meaning of the "clear evidence" requirement. As the Third Circuit observed in *In re Fosamax*, "the number of cases applying the clear evidence standard continues to grow, yet 'the clear evidence standard remains

undefined.'" 852 F.3d at 284 (quoting *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d at 1119).

The *Fosamax* court concluded that *Wyeth* imposed a standard of proof—that is, proof by clear and convincing evidence, rather than by preponderance of the evidence. 852 F.3d at 284-86. Other circuits, however, "have decided preemption cases by simply treating the facts of *Wyeth* as a yardstick: if the evidence for FDA rejection in a given case is less compelling than the manufacturer's evidence in *Wyeth*, the thinking goes, then there is [not] clear evidence that the FDA would not have approved a label change and the manufacturer's preemption defense fails." *Id.* at 284 (citing *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392-96 (7th Cir. 2010); *Gaeta v. Perrigo Pharms. Co.*, 630 F.3d 1225, 1235-37 (9th Cir 2011)). If that is in fact the meaning of "clear evidence," it is an unusually amorphous standard, and not particularly useful to a district court attempting to implement it in a specific case.

In any event, for purposes of deciding the summary judgment motion here, that issue need not be resolved. As set forth below, because there are disputed issues of material fact as to the relevant issues, GSK would not be entitled to summary judgment in its favor even under a straightforward application of a preponderance-of-the-evidence standard. Accordingly, the Court will assume for present purposes, without deciding, that the term "clear evidence" does not impose a higher standard of proof than preponderance of the evidence.

At a minimum, however, the term "clear evidence" implies that a materiality standard should apply to claims based on alleged false statements and omissions to the FDA. If, for example, the allegedly omitted information was cumulative, irrelevant, trivial, or inconclusive, its omission surely was of no consequence. *See Neder v. United States*, 527 U.S. 1, 16 (1999) ("In general, a false statement is material if it has a natural tendency to influence, or [is] capable

of influencing, the decision of the decision-making body to which it was addressed.") (internal quotations omitted).

However, because preemption is an affirmative defense, plaintiffs do not have to show that the information at issue *was* material to defeat preemption. Rather, in order to prevail, GSK would have to show that the allegedly omitted information *was not* material—that is, that it would have made no difference to the decision-maker even if it had been provided.

E. Whether the Standard Is Subjective or Objective

The next question is whether the standard is subjective (that is, what the actual FDA officials at the relevant time would have done) rather than objective (that is, what a reasonable FDA official would have done under similar circumstances). The *Wyeth* opinion does not indicate either way. The Third Circuit in *Fosamax* seemed to suggest that the standard is subjective. *See* 852 F.3d at 290-91 (discussing that the standard concerns what FDA officials "[were] thinking" and what their "motives and thought processes" were). Other courts, however, have suggested that the standard is objective. *See In re Bard IVC Filters Products Liability Litigation*, 2017 WL 6523833, at *8 (D. Ariz. Dec. 21, 2017) (holding that a former commissioner of the FDA "is qualified to opine about what a reasonable FDA official would have done with additional information"); *In re Yasmin and Yaz (Drospirenone) Marketing, Sales Practices, and Products Liability Litigation*, 2011 WL 6302287, at *13 (S.D. Ill. Dec. 16, 2011) (same).

Plaintiffs' claim, in substance, is that GSK made false statements, and omitted important information, in its disclosures to the FDA. Normally, an objective standard is applied in ascertaining the materiality of an alleged false statement or omission. *See, e.g.*, Restatement (Second) of Torts § 538 (1977) ("Reliance upon a fraudulent misrepresentation is not justifiable

unless the matter misrepresented is material. *The matter is material if a reasonable man would attach importance to its existence or nonexistence* in determining his choice of action in the transaction in question . . .") (emphasis added).

Here, the use of an objective standard seems appropriate. That appears to be the more sensible and workable approach, and more consistent with the approach taken in other legal contexts. Furthermore, using a subjective standard adds multiple layers of complication to the fact-finding process. Among other things, the FDA is a complex organization with many different decision-makers, who presumably changed over time; indeed, many of the relevant decisions were rendered nearly thirty years ago. Ascertaining what the state of mind of the relevant regulators would have been, had the disputed disclosures been made, would no doubt be a prolonged and difficult inquiry.

Under the circumstances, the Court will assume that the standard is objective: that is, the issue is the effect the alleged false statements and omissions would have had on a reasonable FDA regulator under similar circumstances.

F. Whether "Fraud-on-the-FDA" Claims Are Not Subject to the *Wyeth* Standard

The next question is whether this case, which is based on a material misrepresentation theory, should be analyzed under a different framework than *Wyeth*. That issue arises out of the interplay of *Wyeth* and the Supreme Court's decision in *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001).

In *Buckman*, plaintiffs claiming injuries resulting from the use of certain orthopedic bone screws brought state-law fraudulent misrepresentation claims against the consulting company that assisted the screw manufacturer in navigating the federal regulatory process for those devices. The plaintiffs alleged that the defendant made fraudulent misrepresentations to the FDA

in the course of obtaining approval to market the screws. They further alleged that had those misrepresentations not been made, the FDA would not have approved the devices, and they would not have been injured. The Supreme Court, however, concluded that those claims were preempted, holding as follows:

> [W]e hold that the plaintiffs' state-law fraud-on-the-FDA claims conflict with, and are therefore impliedly pre-empted by, federal law. The conflict stems from the fact that the federal statutory scheme amply empowers the FDA to punish and deter fraud against the Administration, and that this authority is used by the Administration to achieve a somewhat delicate balance of statutory objectives. The balance sought by the Administration can be skewed by allowing fraud-on-the-FDA claims under state tort law.

531 U.S. at 348 (footnote omitted).

Despite that sweeping language, the *Wyeth* court distinguished *Buckman*, stating that the latter case "involved state-law fraud-on-the-agency claims, and the Court distinguished state regulation of health and safety as matters to which the presumption [against preemption] does apply." 555 U.S. at 565 n.3; *see Buckman*, 531 U.S. at 347-48 ("Policing fraud against federal agencies is hardly 'a field which the States have traditionally occupied,' such as to warrant a presumption against finding federal pre-emption of a state-law cause of action . . . [I]n contrast to situations implicating 'federalism concerns and the historic primacy of state regulation of matters of health and safety' . . . ." (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947); *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). The *Buckman* court contrasted the fraud-on-the-agency claims before it, which arose solely from the defendant's alleged violation of FDA disclosure requirements, with the common-law negligence claims in *Medtronic*, which did not, despite the fact that they paralleled FDA requirements. *See* 531 U.S. at 352-53.

Here, plaintiffs essentially assert state-law failure-to-warn product-liability claims, not state-law fraud-on-the-FDA claims. Those claims are based in large part on GSK's alleged

misrepresentations in violation of FDA disclosure requirements, but are framed as product-liability claims. It therefore appears that *Buckman* does not apply in the present circumstances.

G. Whether Defendants Are Entitled to Summary Judgment

To summarize: (1) preemption is an affirmative defense, as to which GSK bears the burden of proof; (2) preemption presents a question of fact, to be considered on summary judgment like any other factual issue; (3) for present purposes, the Court will not decide whether the standard of proof is clear and convincing evidence, rather than preponderance of the evidence, but the allegedly omitted material must have been material; (4) the standard is objective—that is, what effect the allegedly omitted information would have had on a reasonable regulator; (5) the standard of *Wyeth* applies—that is, to prevail, GSK must show (a) that it could not have changed the label, by the CBE process or otherwise, or (b) if it could, that there is clear evidence that the FDA would have rejected the label that plaintiffs contend state law would have required.

The remaining question is whether, given that framework, GSK is entitled to summary judgment in its favor on preemption grounds.

Plaintiffs do not dispute that the FDA rejected enhanced warning labels on multiple occasions, and that those rejected labels in substance contain the same warnings plaintiffs say GSK should have provided. They contend, however, that GSK could have unilaterally changed its label through the CBE process after the initial label had been approved.[11] They further contend that the FDA's rejection of proposed changes to the label, through the citizen petition and the Novartis application, were based on incomplete evidence, because GSK withheld

[11] 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. According to plaintiffs, had the FDA been presented with that information, it would have required substantially stronger warnings for use during pregnancy.

As set forth above, to prevail, GSK essentially has to show that the CBE process was not available to it or that the FDA would not have approved the proposed label. As to the latter, GSK has to show that the FDA was fully informed as to the relevant science, and that any alleged omission or failure to disclose was not material. In other words, GSK must essentially show that the FDA either had the disputed information, or that the disputed information would not have made a difference had it been provided.

GSK contends, in substance, that it appropriately submitted safety information to the FDA at the relevant times. It further contends that there was no "newly-acquired" data of a "different type or greater severity or frequency than previously included in submissions to [the] FDA" that would have permitted it to submit a label change pursuant to the CBE process. (Def. Mem. at 13-14). GSK also contends that the CBE process could not be used to change the "use in specific populations" language on the label, and that any such change could only be made through a PAS request. (*Id*. at 14-15).

In support of their position, plaintiffs have submitted, among other things, an expert report from Dr. Brian E. Harvey, who served as a Medical Officer/Supervisory Medical Officer at the FDA from 1995 to 2007.[12] As set forth below, the report includes a variety of conclusions as to the completeness of GSK's disclosures and the materiality and likely effect of GSK's alleged omissions.[13]

[12] From 2005 to 2007, Dr. Harvey was Director of the Division of Gastroenterology Products. His report states that in that role, he "was involved with all label negotiations between [his] divisions and the drug sponsors in this therapeutic area, including Zofran." (Supp. and Am. Jenner Decl. Ex. 5 at 4).

[13] GSK has recently filed a motion to exclude Dr. Harvey's conclusions pursuant to Fed. R. Civ. P. 702 and *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993). This memorandum and order assumes without deciding, that Dr. Harvey's opinions are admissible.

1. Japanese Animal Studies

The parties do not dispute that GSK referred to the three Japanese animal studies by title and number in its 1993 Annual Report to the FDA. GSK contends that its disclosure complied with federal regulations, and that "[i]t was [the] FDA's prerogative to accept citations to the publicly available Japanese studies instead of full reports." (Def. Reply Mem. at 5). It further contends that the Japanese studies were not "newly acquired information" within the meaning of the CBE regulations, because they were disclosed to the FDA and did not "reveal risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA." *See* 21 C.F.R. § 314.3.

Plaintiffs dispute that contention, relying substantially on the report of Dr. Harvey, who opined as follows:

> GSK's selection of Pregnancy Category B was based upon four animal reproductive toxicology studies in 1985 in the U.K. However, in 1988, GSK conducted three other animal reproductive studies in Japan, but failed to present the results of those studies to FDA in its application. Instead, on December 23, 1993, GSK reported only the study numbers of the Japanese studies as part of its 1993 annual report to FDA, stating that the studies were "considered not to be relevant to the safety evaluation of [Zofran]."

(Supp. and Am. Jenner Decl. Ex. 5 at 42) (footnotes omitted).

> To the extent any of the results of these [three Japanese] studies showed adverse effects in the drug group that were not seen in the control group, regulatory standards required that GSK submit those studies to FDA. In order to conduct a complete evaluation, FDA must be given the opportunity to have their own toxicologists review all reproductive animal studies to determine whether the adverse effects were treatment related and may have represented signs of developmental teratogenicity. Especially at the time of initial approval, the drug sponsor is expected to submit all known reproductive toxicology studies; it is not allowed under the regulations to choose only those studies that are favorable to the drug sponsor and exclude others that reveal abnormalities.

(*Id.* at 55) (footnotes omitted).

The evidence as to whether GSK complied with then-existing FDA disclosure

requirements when it submitted the study numbers is limited. As noted, 21 C.F.R. § 312.33 requires that annual reports for investigational NDAs 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") (emphasis added). It is unclear whether GSK's filings literally complied with that regulation. Dr. Harvey's report, other than citing to 21 C.F.R. § 312.50 (concerning the content and format of NDAs), simply states in general terms that "regulatory standards" required submission of the full reports, that the drug sponsor is "expected" to submit such reports, and that it is "not allowed under the regulations" to "choose" only "favorable" studies. GSK has submitted no expert or other affidavit in response. Nor does it cite to any specific regulation or FDA policy against which to measure the sufficiency of its disclosures (other than to contend that the full reports from these studies cannot constitute "newly acquired information" within the meaning of 21 C.F.R. § 314.3). It is unclear how the Court could conclude on the present record that the "list" and "summary" provided to the FDA were complete and accurate.

Even assuming that GSK did not properly disclose the information to the FDA, that is not the end of the inquiry, because GSK could show that the allegedly omitted information was not material—that is, that it would have made no difference to the FDA even if it had been provided.[14]

As to that issue, plaintiffs rely principally on Dr. Harvey's expert report, which states the

[14] Of course, even if omitted information was shown to be material—that is, that it might have made a difference—that does not mean it would have resulted in a different outcome. But in the summary judgment context, the court must draw all reasonable inferences in favor of the non-moving party. Thus, if there is evidence sufficient to conclude that the omitted information *could* have made a difference, the Court must assume that it *would* have made a difference.

following:

> GSK had an obligation to disclose the results of all three of these [Japanese] studies to FDA prior to agency approval of the application.
>
> Based upon my agency experience, had GSK done so, FDA would have taken into consideration all seven reproductive toxicology animal studies including the findings of evidence of developmental teratogenicity. Therefore, FDA would not have approved a Pregnancy Category of B for Zofran at the time of initial approval due to knowledge of animal reproductive studies that showed "an adverse effect on the fetus." Knowing there was evidence of fetal harm in animal studies, FDA would have designated Zofran as a Pregnancy Category C.

(Supp. and Am. Jenner Decl. Ex. 5 at 56).

> GSK certainly should have disclosed the study results of all the Japanese animal studies as part of its 1997 NDA application. GSK had multiple opportunities to provide FDA with the full picture of the reproductive toxicology animal studies that were conducted. GSK could have disclosed at least three of the four studies prior to FDA's initial approval [of] Zofran and all four should have been disclosed by the time of GSK's supplement to the NDA at the end of 1991. Had GSK done so, Zofran would not have met the definition of a Pregnancy Category B drug. More recently, FDA would have had the opportunity to change the Pregnancy Category to C in 1999 . . . if GSK had submitted all the Japanese animal studies as required by the regulatory standards. . . . As the Division Director at FDA from 2005 to 2007, [had] this omitted information been brought to my attention, I would have considered it material. If GSK complied with the regulatory standards Zofran would have been designated as a Pregnancy Category C drug and adequate labeling would have included warnings of potential teratogenic effects.

(*Id.* at 59).

As to the rejection of the proposed Novartis labeling change, Dr. Harvey's report includes the following:

> If GSK had properly reported the detailed results of the Japanese animal studies to FDA, they would have been material to FDA's review of a label change and the outcome would have been different from Novartis'[s] attempt to change the label. Novartis's proposed labeling changes were supported only by a safety signal in the adverse events reports. Operating under the assumption that animal studies were negative for teratogenicity, FDA prohibited stronger pregnancy warnings. If FDA had been given the totality of the evidence, they would likely have approved the Novartis proposed labeling change.

(*Id.* at 98) (footnotes omitted).

GSK contends that submission of the full Japanese animal studies would not have been material to the FDA's decision-making, because "GSK gave FDA data on literally thousands of animals that had been exposed to Zofran during preclinical reproductive toxicity studies," and that plaintiffs are "cherry-picking and misinterpreting information" favorable to their claims. (Def. Mem. at 6). It further contends:

> . . . [T]he Japanese animals exposed to Zofran did not reveal risks of a different type or greater severity or frequency than those shown in the wealth of other Zofran preclinical data provided to FDA. Plaintiffs conveniently ignore many other GSK-conducted animal studies---both from the U.K. and Japan---submitted to and reviewed by FDA during the development of Zofran. . . . In fact, FDA's scientists concluded that the preclinical data simply do not show teratogenicity . . . even with results similar to the studies cited by Plaintiffs. Further, the investigators in the Japanese studies determined that there were no teratogenic effects.

(*Id*.). GSK has not, however, submitted an expert or other affidavit to that effect.

Again, GSK has the burden of establishing, as a factual matter, that the requirements of the preemption defense apply. Under the circumstances, it appears at a minimum that there is a disputed issue of material fact as to whether GSK properly disclosed the Japanese animal studies to the FDA, and whether those disclosures would have been material to a reasonable regulator at the agency. The Court therefore cannot conclude, on the present record, that the Japanese animal studies were not "newly acquired information" or would not have revealed "risks of a different type or greater severity or frequency" than previously included in submissions to the FDA, or that there is "clear evidence" that the FDA would have rejected plaintiffs' proposed label changes even if a more comprehensive disclosure had been made.

2. <u>Adverse Event Data</u>

The parties further dispute whether GSK properly disclosed adverse event data to the FDA, and whether that data would have affected the FDA's decision concerning the label.

GSK does not seem to contend that it coded adverse event data appropriately in all respects. Rather, it contends that plaintiffs "incorrectly suggest that the only information GSK provided to FDA about adverse events was in the form of coded lists or disproportionality analyses," and that in truth it "provided far more detailed information to FDA about events reported to it, including pregnancy related events, on a regular basis, as required by the regulations." (Def. Mem. at 9) (footnote omitted). GSK contends (1) that plaintiffs cannot show that some other kind of coding would have revealed an increased risk of birth defects, (2) that the adverse event data in question did not "reveal risks of a different type or greater severity or frequency than previously included in submissions to [the] FDA," and therefore (3) that it had no obligation to use the CBE process to amend the label. *See* 21 C.F.R. § 314.3. Finally, GSK contends that the FDA "wholly discounted the value of adverse events during the label change discussion between Novartis and FDA," stating that "[i]t is not possible to rely on case reports of congenital abnormalities to determine drug attribution given that the background incidence of major congenital abnormalities is 2-4%." (Def. Mem. at 10-11, quoting Ex. 27 at 450). It therefore concludes that there is clear evidence that the FDA would not have approved a label change based on that data.

Again, plaintiffs rely largely on Dr. Harvey's report, which states as follows:

> When assessing a drug's safety and making regulatory decisions, FDA considers adverse event reports as part of the totality of the evidence, including information reported on the mechanism of action, clinical studies, literature and preclinical studies. However, GSK did not report to FDA all the information in its possession related to adverse events among women who used Zofran in pregnancy, nor did GSK's analysis given to FDA of Zofran's use in pregnancy include all adverse events that GSK knew or should have known about, nor did GSK respond forthrightly to FDA's request for full details concerning animal[] reproduction studies or provide adequate information on mechanism of action data. Thus, FDA did not and continues not to have all the available relevant data to assess the safety of Zofran's use in pregnancy.

(Supp. and Am. Jenner Decl. Ex. 5 at 87).

> By failing to accurately monitor, assess and report adverse event reports to FDA, GSK altered the mix of evidence available to the agency and deprived FDA of the ability to evaluate Zofran's pregnancy-related risks based on a complete record. As the former Division Director with responsibility for regulating Zofran, the omitted information was material to me and based on my experience would have been material to a reasonable FDA official performing the same regulatory functions.

(*Id.* at 93). GSK has submitted no expert or other affidavit concerning the issue.

Neither party cites to any specific FDA regulation or policy governing GSK's obligation to code or disclose adverse events in a particular way. Dr. Harvey's opinion simply states in general terms that GSK did not report "all the information in its possession related to adverse event reports," and that GSK's analysis did not include "all adverse events that GSK knew or should have known about." He does not, however, seem to opine that GSK miscoded adverse events in any specific instance, or that the FDA would have taken a different position as to the label had the data been coded differently.

Nonetheless, whatever holes may exist in Dr. Harvey's report, it is not plaintiffs' burden to prove a lack of preemption; GSK has the burden of establishing that the requirements of the preemption defense *do* apply. Again, and at a minimum, it appears that there is a disputed issue of material fact as to whether GSK properly coded and disclosed adverse event data to the FDA, and whether those disclosures would have been material to a reasonable regulator. The Court therefore cannot conclude, on the present record, that the adverse event data was not "newly acquired information" or would not have revealed "risks of a different type or greater severity or frequency" than previously included in submissions to the FDA, or that there is "clear evidence" that the FDA would have rejected plaintiffs' proposed label changes even if a more comprehensive disclosure had been made.

3. Mechanism-of-Action Evidence

Plaintiffs have also alleged that GSK's failure to disclose an accurate description of Zofran's biological mechanism of action was a "material omission." (Pls. Mem. at 17). Plaintiffs essentially contend that GSK knew of the existence of the mechanism-of-action data and did not provide that information to the FDA. Plaintiffs further contend that (1) GSK's failure to disclose that information caused Novartis to discount Dr. Danielsson's evidence of the hERG channel mechanism in its 2015 FDA submission, and (2) a 2016 FDA statement about the lack of such evidence as a basis for rejecting Novartis's request to add a pregnancy warning, taken together, show that the failure to disclose was material.

GSK contends that the hERG channel mechanism proffered by Dr. Danielsson cannot constitute "newly acquired information," because the FDA twice considered his evidence of the mechanism of action, as well as the two studies that he relied on to make his findings, and still concluded there was insufficient data to support a pregnancy warning.

The actual evidence in the record as to this issue is sparse. As to the alleged failure to disclose mechanism-of-action information, Dr. Harvey's report states the following:

> When assessing a drug's safety and making regulatory decisions, FDA considers . . . the totality of the evidence, including information reported on the mechanism of action . . . . However, GSK did not . . . provide adequate information on mechanism of action data. Thus, FDA did not and continues not to have all the available relevant data to assess the safety of Zofran's use in pregnancy.

(Supp. and Am. Jenner Decl. Ex. 5 at 87). Dr. Harvey's report states: "If GSK had used the CBE process to update Zofran's label, FDA likely would have allowed the changes based upon

the evidence of a 'reasonable association' between Zofran and birth defects, including: . . . the available information about Zofran's risk of hERG blocking and QT prolongation . . . ." (*Id*. at 97). Again, GSK has provided no countering affidavit.

Under the circumstances, it again appears, at a minimum, that there is a disputed issue of material fact as to whether GSK properly disclosed information concerning mechanism of action to the FDA.

4. The *Einarson* Birth Defect Study

With respect to the *Einarson* birth defect study, plaintiffs allege that GSK failed to disclose its involvement in the study, as well as the opinions of GSK's scientists that the study was flawed. They also allege that the published study "was missing at least one birth defect adverse event that GSK evaluated in the course of the study and maintained in its own safety data[]base." They contend that because the FDA relied on that study "as evidence that Zofran was non-teratogenic," those omissions "represent[ed] additional information clearly relevant to the question of Zofran's association with birth defects that FDA did not have at the time of any of its ondansetron reviews." (Pls. Mem. at 4, 23-24).

GSK contends that the *Einarson* study cannot be considered "newly acquired information" because the FDA reviewed it, with GSK's role clearly disclosed in the "acknowledgements" section, during the labeling approval process. As to the missing adverse event, GSK contends that the defect in question is not material because it is not an injury alleged by a single plaintiff in this case. (Def. Reply Mem. at 11-12).

As to the *Einarson* study, Dr. Harvey's report states the following:

> . . . GSK possessed information on adverse events that occurred during the Einarson study but were apparently never reported in the study abstracts. Despite having this information, GSK featured excerpts from the Einarson abstract studies in each of its [handouts to healthcare providers regarding Zofran use in pregnancy] from the years

> 2002-2004 (before including an excerpt on the final published version) that represented at various times that the study group revealed "no birth defects." Given GSK's knowledge of birth defects reported in the Einarson study group that were not listed in the Einarson abstracts or final publication, inclusion of the Einarson abstracts in its own, voluntary [handouts to healthcare providers regarding Zofran use in pregnancy] was in violation of [GSK's] guide language requiring Medical Information documents "reflect known information on the subject whether favorable or unfavorable." GSK knew that the Einarson study was deficient, was aware of "known information on the subject" that was "unfavorable" to the company, but chose instead to feature the study as an example of Zofran's safe and effective use during pregnancy.

(Supp. and Am. Jenner Decl. Ex. 5 at 71; *see also id.* at 46-48). Dr. Harvey's report concludes that GSK engaged in "an inconsistent pattern of reporting" birth defects from the *Einarson* study, and opines that the observed birth defects "should all have been reported to FDA." (*Id.* at 91). Dr. Harvey does not, however, seem to opine that GSK violated any regulatory or other requirement of disclosure to the FDA. Again, however, GSK has provided no countering affidavit.

Under the circumstances, it again appears, at a minimum, that there is a disputed issue of material fact as to whether GSK properly disclosed the findings of the *Einarson* study to the FDA.

5. <u>The Use of the CBE Process for "Specific Populations" Language</u>

Finally, GSK contends that the CBE process could not be used to change the "use in specific populations" language on the label, and that any such change could only be made through a PAS Request. (Def. Mem. at 14-15). It bases that contention on the fact that the FDA added the "use in specific populations" section of the label in 2006, and yet "specifically omitted this section of the label as one in which a CBE change could be made" when it revised the CBE regulation in relevant part (apparently in 2008). Because 21 C.F.R. § 314.70(c)(6)(iii)(A) permits CBE changes to "add or strengthen a contraindication, warning, precaution, or adverse reaction," without mentioning the "use in specific populations" section added two years prior,

the reasoning goes, under the regulations a manufacturer could only use the CBE process to change those portions of the label that were specifically enumerated, and not any others. GSK contends that a change to the "use in specific populations" section of the label and pregnancy category status therefore could only be made through a PAS. (Def. Mem. at 15, citing 21 C.F.R. § 314.70314.70(b)(2)(v)). Based on that reading of the regulations, GSK concludes that "a CBE change [to the 'use in specific populations' section] was not even an option for GSK." (*Id.*).

Plaintiffs respond to that contention as follows:

> GSK attempts then to argue that the relocation of "Pregnancy" to the newly-created "Use in Specific Populations" section (post 2006) somehow altered or superseded the CBE regulation in relation to how a pregnancy warning may be changed. The CBE regulation, however, existed long before the creation of the "Use in Specific Populations" addition and was not amended to then preclude changes made to that particular section. The only reference in the CBE regulation to a specific section of labeling is a provision prohibiting unilateral CBE changes to the "Highlights of Prescribing Information" section of the label, as expressed in 21 C.F.R. 201.57(a). *See* 21 C.F.R. § 314.70(c)(6)(iii) (requiring that "Highlights" changes be made by Prior Approval Supplement). Plaintiffs' proposed labeling changes, including the Pregnancy Categorization, do not implicate the Highlights section. . . . Hence, the CBE process was available throughout the lifetime of Zofran and is intended to permit the manufacturer's unilateral strengthening of labeling language consistent with material safety information, pregnancy included.

(Pls. Mem. at 26, n.74).

Based on its review of the relevant language, plaintiffs' reading of the CBE regulation appears to be correct. The FDA did not intend to prohibit changes to that portion of the label concerning "use in specific populations" when it revised the regulation. That conclusion is bolstered by the common-sense view that it is highly unlikely that the FDA intended to prohibit a drug company from making voluntary changes to labels affecting specific vulnerable populations (such as pregnant women), if the company became aware of a risk after initial approval of the drug. To the extent, therefore, that GSK's motion for summary judgment relies on the argument that the CBE process could not be used to revise the "Use in Specific Populations" portion of the

label, it will be denied.

6. Conclusion

In summary, based on the evidence in the record, and drawing all reasonable inferences in plaintiffs' favor, there appear to be disputed issues of material fact concerning the availability of a federal preemption defense. Specifically, on the present record, GSK has not proved, based on the undisputed facts, either (1) that the CBE process was unavailable to it to make more substantial warnings concerning the ingestion of Zofran during pregnancy, or (2) that there is "clear evidence" that the FDA would not have approved a label including such warnings. Accordingly, GSK is not entitled to summary judgment in its favor based on an affirmative defense of federal preemption.

IV. Conclusion

For the foregoing reasons, defendant's motion for summary judgment based on federal preemption is DENIED.

So Ordered.

/s/ F. Dennis Saylor
F. Dennis Saylor IV
United States District Judge

Dated: February 5, 2019