UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

IN RE : ZOFRAN® (ONDANSETRON) PRODUCTS LIABILITY LITIGATION	MDL NO. 1:15-md-2657-FDS This document relates to: All Actions

DEFENDANT GLAXOSMITHKLINE LLC'S MEMORANDUM IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT BASED ON FEDERAL PREEMPTION

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I. INTRODUCTION

Plaintiffs' claims against GSK in this multidistrict litigation already have been considered—and rejected—by FDA. FDA controls what information should or should not be included in a drug manufacturer's label. Here, FDA has directly considered—twice in the last three years—whether GSK's Zofran® label should advise patients and prescribers that use of Zofran® during pregnancy can cause birth defects. On both occasions, FDA concluded that there is insufficient scientific support for a Zofran® birth defect warning. Had GSK added the warnings to the Zofran® label that the Plaintiffs allege GSK should have done, GSK would have acted in direct contravention of FDA's rulings on Zofran®. Plaintiffs here cannot reformulate state tort law and end-run years of FDA decision-making by asking a district court judge or jury to conclude otherwise. Their claims, therefore, are preempted and must be dismissed.

FDA has conducted a thorough, comprehensive, and exhaustive review of the medical and scientific information available as to whether the Zofran® label should have included a birth defect warning. In 2015, in response to a Citizen Petition requesting that FDA order changes to the Zofran® labeling and notify doctors of the purported risk associated with use of Zofran® during pregnancy, FDA explained that a birth defect warning would be scientifically unsupported and thus misleading. FDA noted that there has *never* been sufficient scientific support for the claim that Zofran® causes birth defects, including birth defects such as cleft palate and cardiac defects, which are among the most common injuries alleged by Plaintiffs. Accordingly, FDA adopted the official position that the Zofran® label should not include (or have ever included) any formulation of a birth defect warning.

Consistent with its 2015 decision, FDA the next year expressly rejected the request of Novartis Pharmaceuticals Corporation ("Novartis"), the current Zofran® New Drug Application holder, to add warnings regarding a potential risk of fetal harm—the exact type of warnings

Plaintiffs request here. FDA at the time concluded that [redacted] Thus, a drug manufacturer has already asked FDA to revise the Zofran® label to include a birth defect warning, and FDA said no. The Court should reject Plaintiffs' attempts to ask a federal court to include such a warning and thereby make a decision contrary to FDA's lengthy and exhaustive review of the question.

Despite FDA's repeated analysis of this exact issue, and the lack of any newly acquired information warranting a label change, Plaintiffs claim that the Zofran® label should have warned that use during pregnancy can result in fetal harm in the form of birth defects. As the Supreme Court explained in *Wyeth v. Levine*, under the Supremacy Clause of the United States Constitution, a pharmaceutical company cannot be held liable under state tort law for failing to warn of a particular health risk in a drug label where there exists "clear evidence" that the United States Food and Drug Administration ("FDA") "would not have approved" a labeling change to warn of that risk. 555 U.S. 555, 571 (2009). It is difficult to envision a scenario involving clearer evidence: during the course of this litigation FDA ***rejected the same warning*** Plaintiffs contend state law required. Because Plaintiffs' interpretation of state tort law directly conflicts with the reality of what FDA already has explicitly rejected for inclusion in the Zofran® label, Plaintiffs' claims are preempted and must be dismissed.

II. FACTUAL BACKGROUND

A. Zofran®'s History, Labeling, and Important Role in Treating Patients with Nausea

Marketed under the brand name Zofran®, ondansetron hydrochloride was initially approved 27 years ago, on January 4, 1991. It has been approved for nausea and vomiting associated with chemotherapy and radiation and for postoperative nausea and vomiting. Zofran® works to prevent nausea and vomiting (emesis) by blocking serotonin (known as 5-

hydroxytryptamine, or 5-HT) from binding to a specific serotonin receptor called 5-HT3. *See* Jiang-Hong Ye et al., *Ondansetron: A Selective 5-HT3 Receptor Antagonist and Its Applications in CNS-Related Disorders*, 7 CNS DRUG REVIEWS 199-213 (2001), attached as Ex. 10. Zofran® was a revolutionary discovery, as nausea and vomiting caused by chemotherapy could be so severe that the potentially life-saving treatment had to be discontinued. AE Kidgell et al., *Antiemetic control: 5-HT3 antagonists: Review of clinical results, with particular emphasis on ondansetron*, 17 Cancer Treatment Reviews 311–317 (1990), attached as Ex. 11. Zofran® not only allowed treatment to continue, but it also enabled doctors to use more aggressive chemotherapy.

Including its initial approval in 1991, FDA has approved a total of five Zofran® New Drug Applications ("NDA") submitted by GSK:

1. NDA 20007 – Zofran injection (FDA approved 1991);
2. NDA 20103 – Zofran oral tablet (FDA approved 1992);
3. NDA 20403 – Zofran premixed injection (FDA approved 1995);
4. NDA 20605 – Zofran oral solution (FDA approved 1997); and
5. NDA 20781 – Zofran orally disintegrating tablet (FDA approved 1999).

For each Zofran® NDA submitted to FDA, GSK was required to include "the labeling proposed to be used for [the] drug," "reports of investigations which have been made to show whether or not [the] drug is safe for use and whether such drug is effective in use," and "[a]n integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling." 21 C.F.R. § 314.50(d)(5)(viii); 21 U.S.C. § 355(b)(1). Every Zofran® NDA approval indicated that FDA found the formulation "safe for use under the conditions prescribed, recommended, or suggested

in the proposed labeling thereof" and that the labeling was not "false or misleading in any particular." 21 U.S.C. § 355(d). *See* Ex. 3 (original Zofran® IV approval letter and label).

Until June 30, 2015, FDA regulations classified drugs into five categories of safety for use during pregnancy—A, B, C, D, or X, which describe the evidence available regarding use during pregnancy. After reviewing the available data that GSK provided to FDA in its NDA concerning potential risk to fetuses exposed to Zofran®, FDA determined that pregnancy category B was the appropriate safety classification for all five formulations. *See* Ex. 3, 6–9. Between 1992 and 2016 the "Use in Specific Populations" section of the FDA-approved labeling for intravenous Zofran® has generally stated:

> **Pregnancy; Pregnancy Category B**
>
> Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at intravenous doses up to 4 mg/kg per day 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.

See, e.g., Ex. 3, 7; *see also* 21 C.F.R. § 201.80(f)(6)(i)(b) (2006).[1] The text of the Zofran® IV pregnancy category B designation was consistent with the then-federally mandated language.[2] At

[1] In January 1992, FDA required GSK to make certain changes to the originally approved Pregnancy Category B language in order to strictly conform to the wording provided under federal regulation. Ex. 4. The intravenous labeling was later revised to explain that doses of 4 mg/kg/day is equivalent to "1.4 and 2.9 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, respectively, based on body surface area." *See* Ex. 5 (Zofran® IV labeling approved in November 2012).

[2] As set forth in the federal code, "[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 … labeling" must read as follows:

> "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 U.S.C. § 201.57(c)(9)(i)(A)(2) (2006).

all times GSK marketed Zofran®, the FDA-approved labeling for Zofran® oral solution, tablets, and orally disintegrating tablets contained a pregnancy category B statement that was fundamentally equivalent to the Zofran® IV paragraph above. *See, e.g.*, ex. 3, 5–9.

B. Plaintiffs' Claims Against GSK

The gravamen of Plaintiffs' allegations is that GSK failed to warn of Zofran®'s alleged risk to children whose mothers used Zofran®. Although Plaintiffs' Brand Master Complaint asserts nine state tort law causes of action against GSK—negligence, negligent misrepresentation, negligent undertaking, negligence per se, failure to warn-strict liability, breach of express warranty, breach of implied warranties, fraudulent misrepresentation and concealment, and violation of state consumer protection laws—each rests on the theory that Zofran®'s labeling[3] failed to inform Plaintiffs, doctors, and/or the public of Zofran®'s alleged risks. *See* Brand Master Compl. at ¶ 63 (negligence claim based on "[f]ailing to adequately and correctly warn … of the dangers of Zofran"); ¶ 73 (negligent misrepresentation claim based on "fail[ure] to disclose material facts regarding the safety and efficacy of Zofran"); ¶ 90 (negligent undertaking claim based on GSK's alleged improper undertaking of duty to provide "written and verbal information regarding the use of Zofran for pregnancy-related nausea and vomiting"); ¶ 99 (negligence per se claim based on GSK "negligently market[ing] and label[ing] Zofran"); ¶ 105 (strict liability claim based on lack of "adequate warnings, instructions, and directions); ¶ 116 (breach of express warranties for failure to disclose "serious side effects"); ¶ 122 (breach of implied warranties because GSK failed to advise patients and doctors that Zofran® was not "safe

[3] While Plaintiffs' Complaint refers to the Zofran® product information provided by GSK in varying ways (*e.g.*, "labeling," "product information," "instructions," "marketing"), ***all*** information distributed by a prescription drug sponsor regarding a medication is considered drug "labeling" under the Food Drug and Cosmetic Act. *See* 21 U.S.C. § 321 (m)-(n); *Fulgenzi v. PLIVA, Inc.*, 711 F.3d 578, 581 n.1 (6th Cir. 2013) ("The FDA construes 'labeling' broadly, to include not just the written label associated with the drug, but communications with physicians and other healthcare professionals containing additional warnings….").

and fit for the treatment of pregnancy-related nausea or vomiting"); ¶ 134 (fraudulent misrepresentation based on failure to warn of the "risks and dangers associated with Zofran use during pregnancy"); and ¶ 137 (violation of state consumer protection laws based on "statements concerning the health consequences of Zofran use"). Plaintiffs' Generic Use Master Complaint is substantively identical to the Brand Use Master Complaint, except that it does not include the strict liability or breach of warranty causes of action. *See* Plaintiffs' Master Long Form Complaint and Jury Demand – Generic Ondansetron Use ("Master Generic Complaint") (Dkt. 256).

Although not pled as an independent cause of action, Plaintiffs' Master Complaints contain negligence allegations regarding an alleged failure by GSK to properly test Zofran®. *See* Brand Master Compl. at ¶ 64 (negligence); ¶ 88 (negligent undertaking), and ¶ 93 (negligence per se). A negligent testing claim is at base a variation of an action for failure to warn. Implicit in Plaintiffs' failure to test argument is the belief that, had GSK undertaken the necessary testing, the results would have revealed a need for birth defect warnings, thereby forcing GSK to add birth defect warnings to the Zofran® labeling prior to Plaintiffs use of the drug during pregnancy. *See id.* at ¶ 93; 99 (arguing that GSK is liable for negligence per se because GSK's failure to exercise reasonable care in the testing of Zofran® resulted in GSK continuing to "negligently market and label Zofran"). *See also Metz v. Wyeth, LLC*, No. 8:10–cv–2658, 2011 WL 5024448, at *1 n.1 (M.D. Fla. Oct. 20, 2011) ("[T]he conduct complained of is [the manufacturer's] failure to warn-including the cause of such failure (e.g., lack of testing) and the manner by which [the manufacturer] failed to warn consumers and physicians."); *Kociemba v. G.D. Searle & Co.*, 707 F. Supp. 1517, 1527 (D. Minn. 1989) (recognizing that "a breach of the duty to test cannot by itself cause any injury"). Put differently, Plaintiffs say the Zofran®

pregnancy warnings were inadequate because GSK did not sufficiently test the drug. The failure to test argument is, therefore, indistinct from a failure to warn claim. If Plaintiffs' failure to warn argument falls, so too does the failure to test claim.[4]

III. FDA REGULATIONS FOR DRUG LABELING APPROVAL AND AMENDMENT

To market a new pharmaceutical product like Zofran®, a drug company (the "sponsor") submits an NDA to FDA for review and approval. *See* 21 U.S.C. § 355(a).[5] An NDA is required to provide comprehensive information about the drug, including its formulation, the proposed labeling, and scientific data about its safety and efficacy. *Id.* at § 355(b)(1). FDA will approve a drug for marketing if, and 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 nor misleading in any particular." *Id.* at §§ 355(c)(1)(A); 355(d). FDA meticulously reviews each proposed label, "allowing only information for which there is a scientific basis to be included." 73 Fed. Reg. 49604 (Aug. 22, 2008) ("Before approving an NDA … FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is a scientific basis to be included in the FDA-approved labeling."); 21 U.S.C. § 355; 21 C.F.R. § 314.105(c); *see also Levine*, 555 U.S. at 568 ("The FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label.").

[4] To the extent that Plaintiffs purport to assert a negligent manufacturing defect claim independent of their negligent failure to warn arguments, Plaintiffs' Master Complaints fail to allege how the Zofran® product each plaintiff used during pregnancy differed from GSK's "intended result or from other ostensibly identical units of the same product line." *Perez–Trujillo v. Volvo Car Corp.*, 137 F.3d 50, 53 (1st Cir.1998) (internal quotation marks omitted); *see also* 63 Am. Jur. 2d Products Liability § 535 (2018) ("A 'manufacturing defect' exists when a product deviates, in its construction or quality, from the specifications or planned output in a manner that renders it unreasonably dangerous."). Because Plaintiffs have not properly alleged, much less established, the existence of a manufacturing defect, these claims should be dismissed irrespective of the outcome of GSK's preemption arguments.

[5] Citations in this Motion are to federal laws and regulations currently in effect. A drug sponsor's relevant obligations have been essentially the same since Zofran®'s approval in 1991.

Once a drug is approved, its sponsor generally is prohibited from altering its label without FDA's advance permission. But if significant information arises that materially alters the scientific understanding of a drug's safety or efficacy, an updated label may be immediately necessary. Specifically, sponsors 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(a); 314.70(b)(2). This action, known as the "changes being effected" ("CBE") process, allows a sponsor to make an immediate labeling change upon filing a supplemental application with FDA. The amended label is then subsequently reviewed by FDA and will be approved only 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).

For purposes of the CBE regulation, "newly acquired information" comprises:

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

21 C.F.R. § 314.3. The existence of newly acquired information is a firm prerequisite to any CBE label change. *See In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 41–42 (1st Cir 2015) (citing 21 C.F.R. § 314.70(c)(6)(iii)). Put differently, a sponsor cannot change a drug label to reflect information previously provided to FDA. *See id.* at 48 (rejecting plaintiffs' argument that defendant could have amended label based upon information that was "plainly known to the FDA prior to approving the label"). The CBE regulation further requires that the "newly acquired information" be of a "different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. § 314.3(b).

Although a manufacturer may, under limited circumstances, utilize the CBE process to make immediate labeling changes, FDA still carefully analyzes the amended language as well as the scientific information and data supporting the changes. If the Agency determines that the changes render the drug "misbranded," it may reject the CBE labeling supplement, order the sponsor to cease distributing the drug with the labeling changes, and bring an enforcement action. 21 C.F.R. § 314.70(c)(7); 71 Fed. Reg. 3934 (Jan. 24, 2006) ("While a sponsor is permitted to add risk information … without first obtaining FDA approval via a CBE supplement, FDA reviews all such submissions and may later deny approval of the supplement, and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading….").

A drug is misbranded if its "labeling is false or misleading in any particular." *Id.* at § 352(a), (j). Misbranding is not limited to labeling that fails to warn of a serious hazard; providing too many warnings or warnings not based on sound scientific principles are equally prohibited forms of misbranding. *See* 73 Fed. Reg. 2851 (Jan. 16, 2008) ("Exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug, biologic, or medical device or decrease the usefulness and accessibility of important information by diluting or obscuring it."); *Cerveny v. Aventis*, 855 F.3d 1091, 1102 (10th Cir. 2017) ("FDA views overwarnings as problematic because they can render the warnings useless and discourage use of beneficial medications.").

FDA also independently monitors the adequacy of existing labeling. Federal regulations require that the Agency promptly demand label changes if it "becomes aware of new safety information" that it "believes should be included in the labeling of the drug." 21 U.S.C. §

355(o)(4)(A).[6] Upon notification from FDA, a sponsor has just 30 days to either submit proposed label changes or provide reasons explaining why no update is necessary. *Id.* at § 355(o)(4)(A).

Ultimately, and importantly for the preemption analysis, whether a safety issue is detected by FDA, a sponsor, or a concerned citizen, the same regulatory standard for a label change applies: a new warning is necessary "as soon as there is reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 201.80(e); *see also 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"). As the court observed in *Seufert v. Merck Sharp & Dohme Corp*, the "regulatory standards governing prescription drug labeling are the same whether the FDA is considering data as part of an independent review, in connection with a citizen petition, or in response to a manufacturer submitted CBE." 187 F. Supp. 3d 1163, 1175 (S.D. Cal. 2016).

IV. LEGAL STANDARDS

A. Summary Judgment

Summary judgment is appropriate when "there is no genuine issue as to any material fact and ... the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c). A "genuine" issue is one "that properly can be resolved only by a finder of fact because [it] may reasonably be resolved in favor of either party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 250 (1986). "A fact is 'material' if its existence or nonexistence has the potential to change the outcome of the suit." *Borges ex rel. S.M.B.W. v. Serrano-Isern*, 605 F.3d 1, 5 (1st Cir. 2010). Once the moving party makes an initial showing "that there is no genuine issue of material fact which requires resolution in the crucible of a trial," the burden shifts to the non-moving party to

[6] Congress granted FDA this statutory authority in 2007. Pub. L. No. 110-85, § 355, 121 Stat. 823, 924–926 (2007).

set forth "specific facts … that a trialworthy issue remains." *Cadle Co. v. Hayes*, 116 F.3d 957, 960 (1st Cir. 1997).

B. Federal Preemption

"[F]ederal preemption … presents a pure question of law" and, thus, may be resolved in a motion for summary judgment. *United States v. R.I. Insurers' Insolvency Fund*, 80 F.3d 616, 619 (1st Cir. 1996); *see also Remington v. J.B. Hunt Transp., Inc.*, No. 15-10010, 2016 WL 4975194, at *2 (D. Mass. Sept. 16, 2016) ("Rooted as it is in the Supremacy Clause of the United States Constitution, federal preemption is a 'pure question of law.'") (citing *R.I. Insurers'*, 80 F.3d at 619).[7]

The federal preemption doctrine derives from the Supremacy Clause of the United States Constitution, which provides that federal law "shall be the supreme Law of the Land" and that the state courts "shall be bound thereby, anything in the constitution or laws of any state to the contrary notwithstanding." U.S. Const., Art. VI, cl 2. There are three types of preemption: (1) express preemption, (2) field preemption, and (3) conflict preemption. *Altria Grp, Inc v. Good*, 555 U.S. 70, 76–77 (2008). At issue in this case is conflict preemption, which arises "where compliance with both federal and state regulations is a physical impossibility," *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142–43 (1963), or where the challenged state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of

[7] *Contra In re: Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 852 F.3d 268 (3d Cir. 2017) (holding that "whether the FDA would have rejected a label change is a question of fact"); *but see In re Risperdal® and Invega® Prod. Liab. Cases*, 2017 WL 4479317 (Cal. Super. Ct. 2017) (finding preemption to be a pure question of law and that *Fosamax* was thus "wrongly decided"); *see also* Brief for the United States as Amicus Curiae, *Merck Sharp & Dohme Corp. v. Albrecht*, 2018 WL 2357737, at *12 (May 22, 2018) (advocating Supreme Court review of the Third Circuit's *Fosamax* decision and arguing that [w]here … FDA renders a decision declining to approve a drug labeling change, the interpretation of that administrative decision and its significance for a failure-to-warn claim are legal questions for a court to resolve, not factual questions for a jury"). On June 28, 2018, the Supreme Court granted Merck's petition for a writ of certiorari. *Merck Sharp & Dohme Corp. v. Albrecht*, No. 17-290, 2018 WL 3148288, at *1 (U.S. June 28, 2018).

Congress." *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). "The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011). State laws that demand action unachievable under federal law are "without effect." *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981). "Federal regulations" have as much "preemption effect [as] federal statutes." *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982).

V. PLAINTIFFS' CLAIMS ARE PREEMPTED

The ability to amend a label without prior FDA approval is critical for purposes of a federal preemption analysis. The question for federal preemption is whether a party can *independently* do under federal law what state law requires of it. *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 623–24 (2011) ("[W]hen a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for pre-emption purposes.").

Determining whether Plaintiffs' claims are federally preempted is a two-step inquiry. First, Plaintiffs bear the burden of demonstrating that federal regulations permitted the sought-after CBE label changes. This means that Plaintiffs must show, *inter alia*, that "newly acquired information exists such that the manufacturer could have unilaterally changed its label in accordance with [FDA's Changes Being Effected] regulation." *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644, 672 (S.D.N.Y. 2017). Likewise, CBE labeling changes can merely be made to "add or strengthen a contraindication, warning, precaution, or adverse reaction" 21 C.F.R. § 314.70(c)(6)(iii)(A).[8] Only if Plaintiffs satisfy this burden does the Court reach the second step

[8] Therefore, claims that a drug manufacturer should have, for example, unilaterally amended the indication statement are preempted because an indication labeling change is not permitted under the CBE

and consider whether there is "'clear evidence" that the FDA would have exercised its authority to reject the labeling change." *Utts*, 251 F. Supp. 3d at 672.

GSK's Motion should be granted because Plaintiffs cannot top either hurdle. First, there is no "newly acquired" Zofran® data of a "different type or greater severity or frequency than previously included in submissions to FDA" that could have theoretically allowed GSK to submit a CBE label change. Additionally, federal regulations prohibited GSK from using the CBE process to alter the pregnancy category-based warnings in the Zofran® label. And second, even assuming that Plaintiffs could point to "newly acquired" data or locate an appropriate alternative location for a birth defect warning beside the pregnancy category—which they cannot—clear evidence exists that FDA would have rejected the labeling change Plaintiffs' argue was required. Indeed, FDA already considered and rejected the precise warnings Plaintiffs seek in this MDL.

A. There is No "Newly Acquired" Zofran® Data that Would Have Permitted a Labeling Change.

Plaintiffs' claims should be dismissed because there is no "newly acquired" Zofran® data of a different type or frequency that would have permitted GSK to change the label. Plaintiffs allege that "since at least 1992, [GSK] had mounting evidence showing that Zofran presents an increased risk of harm to babies who are exposed to the drug during pregnancy."[9] Brand Master Compl. At ¶ 60. Yet, Plaintiffs fail to offer *any* examples of the "mounting evidence" that they presumably believe constituted sufficient evidence to warrant a label change.[10] And, to this day,

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process. *See* 21 C.F.R. § 314.70(b)(2)(v) (providing that prior approval is necessary for changes other than those allowed under CBE process and certain other limited circumstances).

[9] Notably, the critical starting date for conflict preemption purposes is not 1992, but instead 1999, the year FDA approved the fifth and final Zofran® formulation—Zofran® ODT. Drug manufacturers can only use the CBE process to amend labeling based on new information not previously submitted to FDA.

[10] Plaintiffs refer generally to adverse event reports received by GSK since 1992 but fail to offer any examples or explain how these reports "reveal risks of a different type or greater severity or frequency

no evidence exists. Any doubt was erased by FDA when it repeatedly concluded, as recently as 2016, that [redacted] Ex. 27 at -4451. Because there is no newly acquired Zofran® data, GSK could not have unilaterally changed the Zofran® label, and Plaintiffs' claims are preempted.

B. Federal Regulations Prohibited GSK from Unilaterally Altering the "Use in Specific Populations" Language in the Zofran® Label

Even if Plaintiffs could point to newly acquired evidence, their claims fail for another reason. Plaintiffs take issue with the language in the "Use in Specific Populations" section of the Zofran® label, including the category B language mandated by federal regulations. Brand Master Compl. at ¶ 51. As an initial matter, federal regulations dictate verbatim what language must be used to describe pregnancy categories in the labeling. *See* 21 U.S.C. § 201.57(c)(9)(i)(A)(2) (2006) (providing that "labeling *must* bear the statement required" for pregnancy category B) (emphasis added). GSK could not have used the CBE process to alter this language.

The FDA further clarified that the CBE process was unavailable to change information related to pregnancy in June of 2006, when it implemented changes to the format of the label,

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than previously included in submissions to FDA." 21 C.F.R. § 314.3. The Supreme Court has cautioned that "[t]he fact that a user of a drug has suffered an adverse event, standing alone, does not mean that the drug caused that event." *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 44 (2011). "[T]he mere existence of reports of adverse events ... says nothing in and of itself about whether the drug is causing the adverse events." *Id.* This is particularly true when considering birth defect reports. As FDA explained to Novartis, "[t]he background incidence of major congenital malformations is 2-4% Therefore, reports of congenital malformations associated with use of Zofran, or other drugs or without any drugs, in the first trimester is expected." Ex. 27 at -4450. The simple fact that there were reports of birth defects in children whose mothers used Zofran® during pregnancy is, therefore, insufficient to establish the requisite newly acquired evidence of a potential causal association. Moreover, as explained above, any adverse event reports made prior to 2000 cannot constitute newly acquired evidence because these reports were submitted to FDA prior to FDA's approval of Zofran® ODT in 1999. 21 C.F.R. § 314.3 (Information is not "new" if "previously included in submissions to FDA"). Even in light of these reports, FDA as recently as 2015 affirmed the Zofran® Pregnancy Category B label language. *See* Citizen Petition Response, Ex. 17 at 18–19.

including adding a new section of the label entitled "Use in Specific Populations," and specifically omitted this section of the label as one in which a CBE change could be made. *See* 21 C.F.R. § 314.70(c)(6)(iii)(A) (permitting CBE changes only to "add or strengthen a contraindication, warning, precaution, or adverse reaction."). Instead, a change to the "Use in Specific Populations" language and pregnancy category status could be made only through a Prior Approval Supplemental Request. *See* 21 C.F.R. § 314.70314.70(b)(2)(v). Because GSK could not independently alter the Zofran® "Use in Specific Populations" section, Plaintiffs' state law claims premised on the alleged inadequacy of this language and Zofran®'s pregnancy category B designation are preempted for the independent reason that a CBE change was not even an option for GSK.

C. Plaintiffs' Claims Are Preempted Under the Clear Evidence Standard

Even assuming that Plaintiffs could point to newly acquired Zofran® data to support a CBE amendment, their claims must still be dismissed because there is clear evidence that FDA would have rejected the birth defect warning Plaintiffs seek. A pharmaceutical manufacturer establishes an impossibility defense if there exists "clear evidence that the FDA would not have approved" a drug label change incorporating language demanded by state law. *Levine*, 555 U.S. at 571 ("[A]bsent clear evidence that the FDA would not have approved a change to [a drug's] label, we will not conclude that it was impossible for [the drug sponsor] to comply with both federal and state requirements.").

The plaintiff in *Levine* developed gangrene in her arm following intravenous injection of Phenergan, an antihistamine used to treat nausea. *Id.* at 559. She alleged that the Phenergan labeling inadequately warned of the danger of gangrene when administered using the "IV-push" method. *Id.* at 560. Wyeth, the drug sponsor, argued that federal law preempted the plaintiff's state law failure-to-warn claims because the record reflected that FDA was aware of similar

incidents that had occurred prior to the plaintiff's injury, and that, in the over 40 years since the drug was approved, FDA had communicated with Wyeth on multiple occasions concerning the content of the Phenergan label. *See id*. at 568–70.

The Supreme Court determined that the facts in *Levine* failed to establish that FDA would have rejected an attempt by Wyeth to alter the Phenergan label to more obviously warn against use of the IV-push method. *Id.* at 573. Although FDA and Wyeth had communicated about methods of administering Phenergan, the Court found that neither FDA nor Wyeth had devoted "more than passing attention" to whether the label should instruct healthcare providers to shun the IV-push method in favor of the allegedly lower risk "IV-drip" method. *Id.* at 572. Importantly, the Court noted that FDA's communications with Wyeth about the Phenergan label were "intermittent," and at no point did Wyeth supply FDA with an "evaluation or analysis" of the alleged IV-push method risks. *Id.* at 571–72. There was also no indication that FDA had itself conducted or considered a scientific analysis of the relative risk of the IV-push versus IV-drip methods. *See id.* Based upon this record, the Court could not conclude that FDA had ever offered its clear opinion on the value of IV-push administration. *Id.* at 572. Therefore, the Court rejected "Wyeth's contention that the FDA would have prevented it from adding a stronger warning about the IV-push method of intravenous administration." *Id.* at 573.

Thus, under the "clear evidence" test enunciated in *Levine*, to decide whether Plaintiffs' failure-to-warn claims against GSK are preempted, this Court should consider whether: i) FDA considered the issue raised by Plaintiffs (*i.e.*, whether the Zofran® pregnancy warning should have warned about the (alleged) risk of birth defects), ii) FDA's consideration entailed a review of "an evaluation or analysis" of the claimed birth defect risk, and (iii) FDA made a decision on the issue.

Unlike the Supreme Court's determination that FDA gave "passing attention" to the risks associated with using Phenergen through the IV-push method, FDA's evaluation of whether birth defects are associated with use of Zofran® during pregnancy has been exhaustive.[11]

1. ***FDA Considered GSK's 2011 Pregnancy Review and Required No Label Changes.***

In December 2010, FDA Director Donna Greibel mailed GSK a letter entitled "Prior Approval Supplemental Request." Ex. 12. The letter informed GSK that [redacted] At the time, there were no FDA-approved drugs indicated for the treatment of nausea and vomiting during pregnancy. *See* Slaughter et al, *FDA Approval of Doxylamine-Pyridoxine Therapy for Use in Pregnancy*, 370 New England J. Med. 1081 (2014), attached as Ex. 13. The review and analysis requested by FDA was to include [redacted]

GSK replied to FDA in April 2011, with the conclusion that [redacted] Ex. 14 at 6. Accompanying its reply, GSK provided a detailed examination of the then-available safety data, including published literature and adverse event reports. *See id.* FDA did not subsequently express any questions or concerns with GSK's analysis and conclusion, and it did not require GSK to make any changes to the Zofran® pregnancy labeling. *See* Ex. 15.

[11] Following *Levine*, courts have refused to find the "clear evidence" standard met where FDA had paid little attention to the specific safety risk at issue. *See Gaeta v. Perrigo Pharm. Co.*, 630 F.3d 1225 (9th Cir. 2011) *cert. granted, judgment vac'd sub nom L. Perrigo Co. v. Gaeta*, 132 S. Ct. 497 (2011) (finding that FDA had reviewed general safety of ibuprofen but had not specifically considered potential for liver damage risk when a patient takes ibuprofen concurrently with other known hepatotoxins); *Reckis v. Johnson & Johnson*, 28 N.E.3d 445, 459 (Mass. 2015), *cert. denied*, 136 S. Ct. 896 (2016) (noting that it was "anybody's guess" whether the FDA would approve the labeling language proposed by plaintiffs).

2. *FDA considered and rejected Zofran birth defect warnings in 2015 when it denied the Reichmann Citizen Petition*

The use of Zofran® during pregnancy was again presented to FDA in January 2013, when James P. Reichmann submitted a citizen petition asking FDA to revise the Zofran® label in light of evidence that Mr. Reichmann believed demonstrated that Zofran® "may lead to adverse maternal and/or fetal outcomes" if ingested during pregnancy. Citizen Petition of James P. Reichmann, attached as Ex. 16.[12] Mr. Reichmann considered the data sufficient to warrant a reclassification of the Zofran® pregnancy risk category from B to category C, D, or X, and an FDA warning to obstetricians and gynecologists that use of Zofran® during pregnancy may lead to "adverse maternal and/or fetal outcomes." *Id.* Mr. Reichmann supplemented the petition five times. *Id.*

On October 27, 2015, FDA denied the petition. FDA's Response to Citizen Petition of James P. Reichmann at 3, attached as Ex. 17 ("Citizen Petition Response"). As part of its thorough analysis, FDA considered "information submitted by [GSK] to support approval of the ondansetron NDA,"[13] "post-marketing drug and device adverse event data," and scientific literature obtained through public submissions and through FDA's own "targeted searches." *Id.*

[12] 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(a)(3). Individuals and organizations can use the citizen petition process to seek changes to prescription drug labeling. *See, e.g.*, FDA, *FDA approves safety labeling changes for fluoroquinolones*, *available at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm500325.htm (mandating drug label changes following citizen petition submission). FDA's approval or denial of a citizen petition constitutes an official agency action. *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d 1108, 1126 (S.D. Cal. 2015) (remarking that "responding to citizen petitions is within the FDA's regulatory authority" and the assessment "represents the FDA's official position"), *vac'd on other grounds*, No. 15-56997, 2017 WL 6030735 (9th Cir. Dec. 6, 2017).

[13] Although FDA referred to a singular ondansetron NDA, GSK had by 2015 submitted NDAs for five Zofran® formulations. *See* discussion *supra* Part II.A.

at 18 n.56.[14] FDA acknowledged that, while Zofran® was not approved for the treatment of nausea and vomiting in pregnancy ("NVP"), it was aware that doctors prescribed the drug for this condition. *Id.* at 3. FDA also remarked that NVP potentially affects up to 90% of pregnant women and can, in extreme cases, threaten the life of the mother and child. *Id.*

Following a review of the "the totality of the available data," FDA concluded:

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

Id. at 18.

Accordingly, FDA refused to order any changes to the Zofran® pregnancy warning label: "We 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.* FDA similarly rejected Mr. Reichmann's request for FDA to notify doctors that use of Zofran® during pregnancy is not safe for the fetus. Such a notification, 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.

3. ***FDA Again Rejected Birth Defect Warnings Proposed by Novartis in 2016.***

Novartis acquired Zofran® from GSK in 2015 and, shortly thereafter, submitted to FDA a proposed update to the Zofran® pregnancy labeling to bring it in line with the new Pregnancy and Lactation Labeling Rule (PLLR), published in December 2014. Ex. 21; *see also* 79 Fed. Reg. 72064–65 (Dec 4, 2014). The PLLR required sponsors of a wide variety of drugs to replace the

[14] In addition to published studies, FDA considered abstracts of unpublished study data, but "determined there was insufficient information to meaningfully interpret the abstract results." Citizen Petition Response at 12 n.30.

content and format of their prescription drug labeling with new subsections that inform consumers in narrative form of the potential risks and benefits of using a prescription drug during pregnancy and lactation.[15] 21 C.F.R. §§ 201.57, 201.80; 79 Fed. Reg. 72064. The PLLR also replaced the five risk categories relating to teratogenicity and pregnancy—A, B, C, D, and X.[16]

Novartis's proposal to FDA, as part of the new format, included new warning language regarding the use of Zofran® during pregnancy. Ex. 21. Specifically, in September 2015, after a flood of television and internet advertisements by lawyers soliciting Zofran® cases,[17] Novartis offered the following possible pregnancy section revisions:

- [redacted]
- [redacted]

[15] For instance, where a pre-PLLR label may have stated only that studies had not demonstrated a particular risk to pregnant women, a PLLR-compliant label will summarize the studies used to reach this conclusion and provide the supporting scientific data. *See generally*, 79 Fed. Reg. 72064–65.

[16] The five categories were intended to classify drugs based upon the types of data available relating to use in pregnancy. Drugs in category A, for example, were those for which adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters). 44 Fed. Reg. 37434–67 (June 26, 1979). At the other end of the spectrum were category X drugs, for which animal studies or human studies have demonstrated fetal abnormalities, and which are contraindicated for use in pregnancy. *Id.*

[17] *See* The Silverstein Group, *Zofran Ad Surge Signals Heightened Litigation Interest*, (March 31, 2015), *available at* http://www.silversteingroup.net/mass-tort-ad-watch-blog/zofran-ad-surge-signal-heightened-litigation-interest (last accessed June 28, 2018), attached at Ex. 18. And by September 2015, Plaintiffs' attorneys had already filed dozens of lawsuits alleging birth defects caused by Zofran®.

- [redacted].

Novartis accompanied its suggested changes with 47-page "clinical overview" document summarizing the data that Novartis believed was sufficient to support its revisions. Ex. 22. The overview referenced much of the same science that Plaintiffs have homed in on during this litigation. For instance, Plaintiffs have questioned numerous GSK company witnesses about the ability of Zofran® to produce QT prolongation and the ability of Zofran® to cross the placental barrier.[18] Novartis addressed both issues in the clinical overview. *Id.* at -2307. Similarly, pre-Master Complaint filings by various MDL Plaintiffs referenced the same epidemiological studies cited in the clinical overview.[19]

Additionally, Novartis provided FDA with a detailed recitation of the then available adverse event data. Ex. 22. As indicated in the clinical overview, [redacted]

[18] *See, e.g.*, June 28, 2017, deposition of Derek Newall at 163:21–168:4, excerpt attached as Ex. 19 (discussing study analyzing presence of Zofran® in fetal tissue); Nov. 17, 2017, Deposition of Lynda Haberer at 127:24–133:4. (discussing QT prolongation), excerpt attached as Ex. 20.

[19] *See, e.g.*, *Fratto v. GlaxoSmithKline*, No. 1:15-cv-13754, Compl. at ¶ 55 (July 9, 2015) (citing Pasternak, Danielsson and Anderson studies), attached as Ex. 29. The Master Complaints make no specific reference to any clinical studies.

[redacted]

FDA rejected Novartis's request, refusing to allow the labeling to even so much as suggest *a possibility* that Zofran® may increase the risk of birth defects or any other fetal harm. *See* Ex. 23. More specifically, the Agency removed altogether the paragraph that included the sentence, [redacted] FDA also deleted the [redacted] subsection in its entirety, explaining that [redacted]

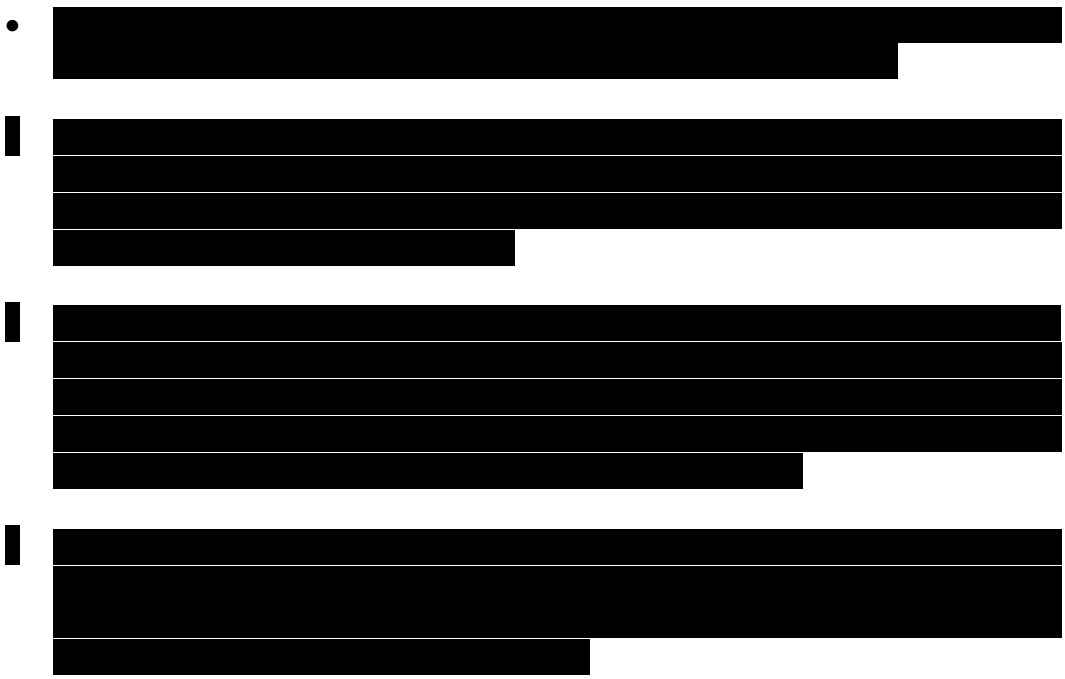
Following FDA's revisions, Novartis submitted a new round of proposed PLLR label changes in December 2015, [redacted]

[redacted]

In its April 2015 response, FDA once more nixed the caution that [redacted] Ex. 25 at -4052. [redacted]

Following FDA's April 2015 revisions, Novartis and FDA engaged in two more rounds of edits before reaching a final, mutually agreed-upon label in September 2016. *See* Ex. 26; 27. FDA made its position clear to Novartis during the discussions relating to the company's proposed PLLR pregnancy labeling in stating:

- [redacted]
- [redacted]
- [redacted]
- [redacted]



The final 2016 version of the Novartis PLLR label, like the predecessor GSK-sponsored labels, advises doctors and patients that the current science does not reliably indicate a potential risk of harm to fetuses exposed to Zofran®: "[a]vailable data do not reliably inform the association of ZOFRAN and adverse fetal outcomes." Ex. 28. The label also maintains that animal study data did not show any significant effects on fetal development other than a slight decrease in maternal body weight for rabbits. *Id.*

4. ***FDA's Repeated Rejection of the Same Warning Plaintiffs Seek in this MDL Easily Satisfies the "Clear Evidence" Standard.***

Since the Court last considered preemption, the features weighing in favor of preemption have only grown. In its January 2016 decision on GSK's motion to dismiss all claims on preemption grounds, the Court deemed the motion as premature for three reasons: 1) the "clear evidence" standard contemplated, in the context of this case, "some opportunity to develop the facts;" 2) Plaintiffs needed a chance to "develop the record as to how the FDA would have responded to a [labeling change] proposal had GSK submitted one;" and 3) it was then unclear

what difference there was between the Zofran® birth defect warnings Plaintiffs believe GSK should have added and the warnings rejected by FDA in response to the Reichmann citizen petition.

The past two and a half years of discovery have afforded Plaintiffs ample opportunity to develop the facts in this case. The over four million documents produced to date—in particular, those pertaining to FDA's actions in 2011, 2015, and 2016—undeniably demonstrate that the Agency finds no basis for Plaintiffs' suggestion that Zofran® may cause congenital defects, and would have rejected any effort by GSK to say so in the Zofran® labeling, regardless of the birth defect warning language GSK might have proposed.

These actions easily surpass the *Levine* clear evidence standard. Indeed, numerous federal courts interpreting the clear evidence standard have found failure-to-warn claims against drug sponsors preempted where the facts showed that FDA had considered the precise safety risk at issue in the litigation and then dismissed the need for labeling changes addressing that alleged risk. *See, e.g.*, *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010) (remarking, "[t]he 'clear evidence' in this case is the agency's refusal to require a reference to SJS/TEN on the label of over-the-counter drugs containing ibuprofen, when it had been asked to do so in a submission to which the agency was responding"); *Seufert v. Merck Sharp & Dohme Corp*, 187 F. Supp. 3d 1163, 1173–74 (S.D. Cal. 2016) (holding "clear evidence exists that the FDA would have rejected a pancreatic cancer labeling change [because …] FDA has consistently considered pancreatic cancer risk and concluded evidence of a casual association was indeterminate"); *Rheinfrank v. Abbott Laboratories., Inc.*, No. 1:13-cv-144, 2015 WL 4743056, at *766 (S.D. Ohio Aug. 10, 2015) (concluding that FDA's denial of two requests to update the defendant's drug label constituted "clear evidence" that FDA would have rejected the labeling

change plaintiffs argued was required by state law); *Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1280 (W.D. Okla. 2011) (holding failure-to-warn claims preempted where FDA had rejected citizen petitions for drugs within the same SSRI class and concluded there existed no evidence of a causal association between these types of drugs and increased suicidality).

Like Plaintiffs here, the claimants in *Cerveny v. Aventis, Inc.* alleged that the defendant drug manufacturer should have warned of an alleged birth defect risk associated with its product, despite FDA's recent rejection of a citizen petition where "FDA analyzed claims and data virtually identical to those submitted by the [plaintiffs]." 855 F.3d 1091, 1105 (10th Cir. 2017). The Tenth Circuit found that the facts presented "a perfect example" of when "the rejection of a citizen petition may constitute clear evidence that the FDA would have rejected a manufacturer-initiated change to a drug label." *Id.* Because FDA "concluded that warnings were unjustified for risks in taking [defendant's drug] prior to pregnancy" the Tenth Circuit recognized that the "conclusion controls" against the plaintiffs' state law tort claims, rendering them preempted by federal law. *Id.*

Considering also FDA's later rejection of birth defect warnings proposed by Novartis, this case presents an even more compelling case for "clear evidence" than did the "perfect example" of facts presented to the Tenth Circuit in *Cerveny*: not only has FDA analyzed citizen petition claims and data virtually identical to those submitted by Plaintiffs, it has actually denied a manufacturer-proposed label change seeking to add any birth defect warnings. As previously explained, FDA judged that [redacted] *Id.* (emphasis added); *see also* 21 CFR § 201.57(c)(6) (requiring "reasonable evidence of a causal association" for a warning).

FDA's statements to Novartis during the labeling change negotiation process confirm that the Agency would not have accepted *any* iteration of a birth defect warning if previously proposed by GSK. Among the variety of birth defect warnings proposed by Novartis and rejected by FDA were that [redacted] The approved labeling now instead advises prescribers that "[a]vailable data do not reliably inform the association of ZOFRAN and adverse fetal outcomes," that "there is no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate," and that there are "[i]mportant methodological limitations" to the single cohort study that reported an association between ondansetron exposure and cardiac septal defect.

In their Master Complaints, Plaintiffs allege that GSK failed to warn of birth defect risks "despite their knowledge that: (a) the safety of Zofran for use in human pregnancy has not been established, (b) there have been reports of birth defects associated with Zofran use during pregnancy, and (c) the weight of the available evidence establishes and increased risk of birth defects." Point (a) can be summarily dismissed. At all times GSK manufactured Zofran®, the labeling indicted that "[t]here are … no adequate and well-controlled studies in pregnant women." For point (b), FDA repeatedly rejected Novartis' attempt to so advise of birth defect reports of on account of the fact there is no scientific basis to believe a causal relationship exists between birth defects and the use of Zofran®. And for point (c), there can be no doubt that FDA disagrees with Plaintiffs' position on the weight of the evidence. Through both its rejection of the Reichmann Citizen Petition and its labeling decisions regarding Novartis, FDA has clearly and consistently expressed the position that there is insufficient evidence to warrant concern about the role of Zofran® in the formation of any type of birth defect. In all, there is simply no

evidence supporting Plaintiffs' claim that FDA would have at any time since 1991 permitted GSK to add any form of birth defect warning to the Zofran® label.[20] Rather, what FDA's Zofran® review unequivocally demonstrates is that GSK's Zofran® pregnancy risk warnings were never false, misleading, or inadequate in any particular.

Because FDA would not have allowed GSK to amend the Zofran® label (and, in fact, regulations expressly forbade GSK from adding scientifically unsupported birth defect warnings), Plaintiffs' state law failure-to-warn claims conflict with federal law and must yield as preempted.

VI. CONCLUSION

FDA's unwavering conclusion is clear: there is insufficient evidence to warrant any form of Zofran® birth defect warning. Not only has FDA dismissed a citizen petition calling for Zofran® birth defect warnings, it has actually *prohibited* any suggestion in the Zofran® label that a causal connection between Zofran® use and fetal harm exists. Whether FDA "would have approved" Zofran® birth defect warnings is, therefore, not a hypothetical question. Additionally, besides FDA's own conclusion that a Zofran® birth defect warning is scientifically unsupported and could be actually be misleading, federal regulation barred GSK from (1) amending the label without "newly acquired information" supporting a change; and (2) from using the CBE process to alter the pregnancy category-based language in the Zofran® label.

[20] Logic compels the conclusion that, if FDA prohibited Novartis' proposed Zofran® birth defect warnings in 2016, then it would have rejected a birth defect warning at any earlier date, when a less comprehensive body of experience, research and analysis existed. *See Rheinfrank v. Abbott Labs., Inc.*, 119 F. Supp. 3d 749, 769 (S.D. Ohio 2015), *aff'd*, 680 F. App'x 369 (6th Cir. 2017) (holding that because FDA rejected defendant's proposed label change in 2005, "it likely would have rejected an earlier-submitted CBE seeking to add the same language to the label"). For this reason, the state law failure-to-warn-based claims of every Plaintiff in this MDL are preempted, as they all involve GSK's alleged lack of action only up through 2015, when it divested Zofran® to Novartis.

For these reasons, GSK respectfully requests that this Court enter an order granting its Motion for Summary Judgment and dismissing Plaintiffs' claims with prejudice.

Dated: July 2, 2018

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CERTIFICATE OF SERVICE

I hereby certify that the foregoing document, which was filed with the Court through the CM/ECF system, will be sent electronically to all registered participants as identified on the Notice of Electronic Filing ("NEF") and paper copies will be sent via first class mail to those identified as non-registered participants.

/s/ Jennifer Stonecipher Hill
Jennifer Stonecipher Hill