UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

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

SAYLOR, C.J.

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

I. Introduction

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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