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 Cases	)	

MDL Order No. 9
January 22, 2016

MEMORANDUM AND ORDER ON DEFENDANT'S MOTION TO DISMISS ALL CLAIMS ON PREEMPTION GROUNDS

SAYLOR, J.

This multi-district litigation arises out of claims that the use of the drug Zofran (ondansetron) by pregnant women caused birth defects. Defendant GlaxoSmithKline, LLC has moved to dismiss all complaints on the grounds that any state-law failure-to-warn claims are preempted by federal law under *Wyeth v. Levine*, 555 U.S. 555 (2009), and that any remaining claims are preempted under *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001).

On October 13, 2015, pursuant to 28 U.S.C. § 1407, the Judicial Panel on Multidistrict Litigation transferred twelve cases to this Court for consolidated pre-trial proceedings as MDL No. 2657. Since that time, at least 196 additional cases have been added by follow-on transfer orders. The Court appointed lead counsel for the plaintiffs on November 18, 2015, and appointed a plaintiffs' steering committee on December 16, 2015.

GSK filed this motion to dismiss on December 11, 2015, before the start of discovery. Plaintiffs oppose the motion on the merits and on the ground that the motion is not procedurally ripe at this stage of the litigation. The Court first requested briefing from the parties only as to the latter issue, and it is that issue—and not the merits of the motion—that is the subject of this

AUTHENTICATED U.S. GOVERNMENT INFORMATION GPO

memorandum and order. For the following reasons, defendant's motion to dismiss will be denied without prejudice to its renewal at a later time.

I. Background

Unless otherwise noted, the following facts do not appear to be in dispute for the purposes of this motion.

Defendant GlaxoSmithKline manufactures the drug ondansetron under the brand name "Zofran." Zofran was first approved in 1991 for the prevention of post-operative nausea and vomiting associated with anesthesia, and for nausea and vomiting caused by radiotherapy and chemotherapy. In addition to those approved uses, GSK is alleged to have marketed Zofran "off-label" for pregnancy-related nausea and vomiting, otherwise known as "morning sickness."

Plaintiffs allege that Zofran was in fact unsafe for use in pregnant women, and that *in utero* exposure to Zofran caused birth defects in children born to mothers who took the drug. GSK characterizes plaintiffs' legal claims as falling into one of two categories: (1) claims that GSK failed to provide adequate warnings of the dangers of Zofran use by pregnant women; and (2) claims that GSK failed to comply with Food and Drug Administration regulations by either marketing Zofran off-label or by withholding information from the FDA. (Def. Mem. 4-5).

GSK has moved to dismiss all claims in all cases, regardless of the applicable state law. In substance, GSK contends that plaintiffs' failure-to-warn claims are preempted in their entirety by federal law in accordance with *Wyeth v. Levine*, 555. U.S. 555 (2009). GSK further contends that any other claims, including those for unlawful off-label marketing activities and concealing safety information from the FDA, are preempted under *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001).

In January 2013, an individual named James Reichmann submitted a "citizen petition" to

the FDA.[1] The petition requested, among other things, that the FDA reclassify ondansetron from pregnancy risk category B to pregnancy risk category C, D, or X "after evaluation of 'new safety information.'" (Def. Mem. Ex. D).[2] Had the FDA approved the petition, the reclassification of ondansetron would have required new, stronger language in the drug's labeling warning of the potential risks associated with its use by pregnant women. *See* 21 C.F.R. § 201.57(c)(9)(i)(A)(3-6) (2006).[3]

The FDA, however, rejected that request in a response issued October 27, 2015. (Def. Mem. Ex. A). The FDA's response was 20 pages long and included, among other things, a review of various studies and scientific literature. It concluded as follows:

> Based on our review of the Petition, supplements, additional submissions to the docket, and the scientific literature, as well as our review of other pertinent data and information, including published literature not referenced in the Petition, supplements, or docket, and adverse event reporting information, we deny the requests in the Petition for the reasons discussed above.
>
> Although we have denied your requested actions, we nevertheless appreciate the information you provided. We will continue to monitor information regarding the use of ondansetron during pregnancy. As with all drug products, we will continue to engage in postmarketing surveillance and review other safety data regarding ondansetron and take any actions as appropriate.

(Def. Mem. Ex. A at 20).

---

[1] A "citizen petition" is a procedural method by which an individual citizen may request that the FDA change or strengthen drug labels. *See* 21 C.F.R. § 10.30.

[2] At the time of the petition, FDA regulations classified drugs into five categories of risk for use during pregnancy. 21 C.F.R. § 201.57(c)(9)(i)(A) (2006). The category chosen dictates the language that must be used in the drug's label. *Id.*

[3] The petition also requested that the FDA

> Notify obstetricians and gynecologists (OB/GYNs) that there is insufficient scientifically acceptable evidence that ondansetron is associated with improved treatment outcomes and may lead to adverse maternal and fetal events or outcomes; [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.

(Def. Mem. Ex. D).

II. **Preemption under *Wyeth v. Levine***

GSK first contends that plaintiffs' state law failure-to-warn claims are preempted by federal law under *Wyeth v. Levine*, 555 U.S. 555. In *Levine*, a patient brought a claim under state law alleging that Wyeth, the manufacturer of the brand-name drug Phenergan, failed to provide adequate warnings in its label of the dangers of administering the drug through an "IV-push." *Id.* at 558. In response, Wyeth argued that the failure-to-warn claim was preempted because it was impossible to comply with both the duties imposed on it by state law and the labeling requirements imposed by the FDA. *Id.* at 567.

The Supreme Court disagreed, and found that Levine's failure-to-warn claim was not preempted. In doing so, the Court relied heavily on 21 C.F.R. § 314.70(c)(6)(iii), commonly referred to as the "Changes Being Effected" ("CBE") regulation. *See Levine*, 555 U.S. at 568-72. The CBE process allows a manufacturer to make changes to its label without prior FDA approval as long as the change reflects "newly acquired information." 21 C.F.R. § 314.70(c)(6)(iii). A change made under the CBE regulation must also be made for one of five specific purposes, one of which is "[t]o add or strengthen a . . . warning." *Id.* The Supreme Court noted that the manufacturer of a brand-name drug bears "ultimate responsibility for its label," and that the CBE process "provides a mechanism for adding safety information to the label prior to FDA approval." *Levine*, 555 U.S. at 571. The Court also noted, however, that the FDA retained the authority to disapprove of a labeling change made by a manufacturer under the CBE regulation. *Id.* Balancing Wyeth's ability to change the Phenergan label pursuant to the CBE and the FDA's ability to reject such a change, the Court held that "absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.*

Thus, when a manufacturer asserts the affirmative defense of preemption under *Wyeth*, a

district court must decide whether "clear evidence" exists that, at the time of the plaintiff's injury, had the manufacturer proposed a change to its label under the CBE regulations, the FDA nonetheless would have rejected that proposal. If the answer is yes, then compliance with both state-law duties and FDA regulations would have been impossible for the manufacturer, and the plaintiff's claim for failure-to-warn under state law is therefore preempted.

In the usual case, the issue is "necessarily fact-specific," requiring the court to weigh the evidence submitted by both sides in an attempt to answer the hypothetical question posed by *Levine*. *In re Incretin-Based Therapies Prods. Liability Litig.*, 2015 WL 6912689, *4 (S.D. Cal. Nov. 9, 2015) (citing *Koho v. Forest Labs, Inc.*, 17 F. Supp. 3d 1109, 1118 (W.D. Wash. 2014)). Here, however, GSK contends that the issue is not hypothetical, because the FDA has already issued a decision concerning the adequacy of ondansetron warnings in response to a citizen petition. In effect, GSK argues that the Court need not consider evidence of how the FDA *might* have answered a change request, because the petition response itself contains the *actual* answer. GSK's position, however, is problematic for at least three reasons.

First, the relevant standard under *Levine* uses the phrase "clear evidence." Whatever the contours, in this context, of the word "evidence," it surely contemplates some form of fact-based evaluation. The Court is reluctant to issue a ruling on a motion to dismiss without giving the plaintiffs some opportunity to develop the facts, whatever those facts may be.

Second, GSK's position is premised on a perhaps slight, but nonetheless potentially material, mischaracterization of the inquiry required under *Levine*. GSK frames the question as whether the "FDA 'would not have approved' the warning that Plaintiffs allege state law required." (Def. Mem. at 1). That formulation of *Levine's* holding is not entirely accurate; it overlooks the mechanism by which a label change is requested and equates a change requested by a citizen petition with one requested by the manufacturer under the CBE regulation. *See*

Miller v. Smithkline Beecham Corp., 381 F. App'x 776, 778 (10th Cir. 2010) ("After *Levine*, GSK must demonstrate . . . 'clear evidence' that the FDA would have rejected GSK's labeling change had it unilaterally strengthened [the drug's] warning label using the CBE supplement.").

The identity and process by which a labeling change is requested may be material because the procedural method used could affect the FDA's response to the proposed change. If—as plaintiffs allege—GSK was in exclusive possession of information not previously submitted to the FDA indicating the need for a new or strengthened warning, that information would presumably be included in a CBE request.[4] That information could not, however, have been submitted by a citizen petition, as no citizen (according to plaintiffs) had access to it. Thus, although the FDA's response to the Reichmann petition is surely relevant to the question of how the FDA might have responded to a CBE proposal, that response does not directly answer the exact question posed by *Levine*. Without commenting on the merits, plaintiffs are entitled to an opportunity to develop the record as to how the FDA would have responded to a proposal had GSK submitted one.

Third, it is not clear at this stage how the warning or warnings plaintiffs allege GSK should have provided compare (or conflict) with the label changes and warnings rejected by the FDA in its response to the Reichmann petition. If there is a difference, it may be material to the relative likelihood of the FDA's approval or rejection of a CBE submission paralleling the warnings plaintiffs allege should have been made.

Accordingly, GSK's motion to dismiss plaintiffs' state law failure-to-warn claims appears to be premature at best, and will be denied without prejudice to its renewal at a later

[4] A CBE submission must be premised on "newly acquired information," which includes "information not previously submitted to the Agency." 21 C.F.R. § 314.3(b). The Court assumes that if GSK had attempted to make a change under the CBE regulation, it would have done so in good faith and made any such information available to the FDA as part of its submission.

date.

III. ***Buckman* Preemption**

GSK next contends that plaintiffs' other claims (that is, those that are not based on a failure-to-warn theory) are preempted under *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001). In *Buckman*, the Supreme Court held that state law "fraud-on-the-FDA" claims were preempted by the Food Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, because such claims "conflict with the FDA's responsibility to police fraud." *Id.* at 350. "Under *Buckman*, a state law claim is not preempted by the FDCA (1) if it only incorporates but does not rely entirely upon an FDCA violation, and (2) if the claim is founded on conduct that would otherwise give rise to liability under state law." *Williams v. Zimmer U.S. Inc.*, 2015 WL 4256249, at *6 (E.D.N.C. July 14, 2015) (citing *In re Bayer Corp. Combination Aspirin Prods. Mktg. & Sales Practices Litig.*, 701 F. Supp. 2d 356, 369 (E.D.N.Y. 2010).

GSK contends that all of plaintiffs' remaining claims—that is, all claims in all cases that are not state-law "failure-to-warn" claims—should be dismissed under *Buckman*. There are currently more than 200 cases in this MDL proceeding. It appears that resolving the issue in the present context (among other things, in the absence of a master complaint) would require evaluating each individual claim in each individual case, identifying the state law that should apply, and assessing whether the claim relies entirely on an FDCA violation or whether it is "founded on conduct would otherwise give rise to liability" under that state's law. *Id.*

The Court is unwilling to undertake the task of sorting out *Buckman*'s applicability to each claim at this stage—especially where the parties have devoted a total of only three pages of briefing to the issue—and without having resolved the preemption issue under *Levine*. It may well prove to be the case that a substantial number of claims will fail on that ground, but the resolution of that question must await another day. Therefore, defendant's motion to dismiss

plaintiffs' claims as preempted under *Buckman* will also be denied without prejudice to its renewal.

IV. Conclusion

For the foregoing reasons, the issues presented in defendant's motion are not ripe for decision on the present record and at this stage of the litigation. Defendant's motion to dismiss is therefore DENIED without prejudice to its renewal at a later date.

So Ordered.

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

Dated: January 22, 2016